A publication of Oncotherm

June 2014
Volume 10.
ISSN 2191-6438

ONCOTHERMIA JOURNAL

The 32nd Annual Conference of the International Clinical Hyperthermia Society (ICHS)*

Specialist Papers
ICHS Conference Papers
ICHS Papers

Hindawi Publishing Corporation
Conference Papers in Medicine

Hyperthermia as an Integrated Cancer Therapy

www.Oncothermia-Journal.com

Editorial

Dear Reader,

shortly before the summer holidays everyone is still busy with a lot of work and interesting events. As usual, the season for conferences started in May with a quite large number of important events: The CIMT conference and Landenberger congress took place in Germany, the annual STM and ASCO meetings were organized in the USA and the 7th Annual World Cancer Congress was visited by many interested people in China. The yearly ESHO conference in Italy followed these in June and the DEGRO conference in Germany will do so in July. Oncotherm was of course present with talks and booths and sponsored many of the listed events. After July there will be a short break before our journeys in order to make Oncothermia internationally known and available to go on. We wish everyone a relaxing summer time in August. The most important events in the second half of the year will be: The 6th Asian Congress of Hyperthermic Oncology in Japan and the ESMO Congress in Spain in September, the Medical Week in Germany in October and the Annual ICHS Conference in Israel in November/December.

As you know Oncotherm works closely together with the International Clinical Hyperthermia Society (ICHS). In 2012 the annual conference was held together with the International Oncothermia Symposium and it will be the same again this year. We believe that this international cooperation will strengthen the network of Hyperthermia users and support the exchange of information and experience between doctors worldwide. The Hyperthermia users are a small group compared to other medical disciplines' users. Therefore, it is more than important that we gather our strength and stand together to represent our treatments that are a very important opportunity for the patients in need and a strong column in the fight against cancer.

We would be happy to see many of you in Israel for the coming conference. You can find all information about the event at the end of this journal. In this issue we present you a large number of abstracts from the last ICHS conference that was beautifully arranged by former president Prof. Dr. Clifford L.K. Pang and came out to be a perfectly organized and professional conference with hundreds of participants from all over the world. We hope that this year's conference organized by the ICHS president Dr. Joseph Brenner will be a further success, increasing hyperthermia's popularity in oncology worldwide. Apart from the conference contents we are presenting you papers that were published in cooperation with Hindawi Publishing, a very interesting poster from Canada about Hyperthermia as Integrated Cancer Therapy, two portraits of new Oncotherm users and of course information on new Oncotherm developments.

I hope you'll enjoy reading.

Sincerely,

Prof. Dr. András Szász

Liebe Leser,

kurz vor den Sommerferien sind wir immer noch sehr beschäftigt mit der täglichen Arbeit und interessanten Veranstaltungen. Wie gewöhnlich hat die Saison für Konferenzen im Mai mit einer großen Anzahl an bedeutenden Events begonnen: Die CIMT Konferenz und der Landenberger Kongress haben in Deutschland stattgefunden, die jährlichen STM und ASCO Treffen wurden in den USA organisiert und der 7. Annual World Cancer Congress wurde von vielen Interessenten in China besucht. Die jährlich stattfindende ESHO Konferenz folgte im Juni in Italien und die DEGRO Konferenz in Deutschland im Juli. Oncotherm war natürlich mit Vorträgen und dem Messestand präsent und hat viele der genannten Veranstaltungen gesponsert. Nach Juli findet eine kurze Pause statt, bevor wir uns wieder auf Reisen machen, um die Oncothermie weltweit bekannt und zugänglich zu machen. Wir wünschen Ihnen allen im August eine erholsame Sommerzeit. Die wichtigsten Veranstaltungen in der zweiten Jahreshälfte sind: Der 6. Asian Congress of Hyperthermic Oncology in Japan und der ESMO Kongress in Spanien im September, die Medizinische Woche in Deutschland im Oktober und die jährliche ICHS Konferenz in Israel im November/Dezember.

Wie Sie wissen arbeitet Oncotherm eng mit der International Clinical Hyperthermia Society (ICHS) zusammen. In 2012 fand die Jahreskonferenz gemeinsam mit dem Internationalen Oncothermie Symposium statt und so wird es auch in diesem Jahr sein. Wir glauben, dass diese internationale Kooperation das Netzwerk der Hyperthermieanwender stärken und den Austausch von Informationen und Erfahrung weltweit unterstützen wird. Im Vergleich zu anderen Disziplinen stellen die Hyperthermieanwender eine kleine Gruppe dar. Umso wichtiger ist es, dass wir unsere Stärke bündeln und gemeinsam unsere Therapien repräsentieren, die eine wichtige Option für Patienten und eine starke Säule im Kampf gegen den Krebs sind.

Wir würden uns sehr freuen, möglichst viele von Ihnen bei der Konferenz in Israel begrüßen zu dürfen. Sie können alle Informationen zur Veranstaltung am Ende dieses Journals finden. In dieser Ausgabe präsentieren wir Ihnen eine große Anzahl an Abstracts von der letzten ICHS Konferenz, die vom letzten Präsidenten Prof. Dr. Clifford L.K. Pang sehr schön arrangiert wurde und eine perfekt oranisierte Konferenz für hunderte Teilnehmer aus aller Welt war. Wir hoffen, dass die diesjährige Konferenz, die von ICHS Präsident Dr. Joseph Brenner veranstaltet wird, ein weiterer Erfolg wird und die Populartät der Onkologie weltweit steigern kann. Abgesehen von den Konferenzinhalten präsentieren wir Ihnen Artikel, die in Kooperation mit Hindawi Publishing veröffentlicht wurden und ein sehr interessiantes Poster aus Kanada zum Thema "Hyperthermia as Integrated Cancer Therapy", zwei Portraits von neuen Oncothermie-Anwendern und natürlich Informationen zu neuen Oncotherm Entwicklungen.

Ich wünsche Ihnen viel Spaß beim Lesen!

Mit den besten Grüßen

Prof. Dr. András Szász

As the editorial team we are committed to a firm and coherent editorial line and the highest possible printing standards. But it is mainly you, the author, who makes sure that the Oncothermia Journal is an interesting and diversified magazine. We want to thank every one of you who supports us in exchanging professional views and experiences. To help you and to make it easier for both of us, we prepared the following rules and guidelines for abstract submission.

Als redaktionelles Team vertreten wir eine stringente Linie und versuchen, unserer Publikation den höchst möglichen Standard zu verleihen. Es sind aber hauptsächlich Sie als Autor, der dafür Sorge trägt, dass das Oncothermia Journal zu einem interessanten und abwechslungsreichen Magazin wird. Wir möchten allen danken, die uns im Austausch professioneller Betrachtungen und Erfahrungen unterstützen. Um beiden Seiten die Arbeit zu erleichten, haben wir die folgenden Richtlinien für die Texterstellung entworfen.

1. Aims and Scope

The Oncothermia Journal is an official journal of the Oncotherm Group, devoted to support them, making a collective for using the results and making it common for general use. The Oncothermia Journal has an open-minded character, expecting the complete study-papers, case-reports, reviews, hypotheses, opinions, and all the informative materials which could be helpful for the international Oncotherm community. Advertisement connected to the topic is also welcome.

- *Clinical Studies:* Regional or local or multilocal oncothermia or electro cancer therapy (ECT) treatments, case-reports, practical considerations in complex therapies, clinical trials, physiological effects, Oncothermia in combination with other modalities, and treatment optimization.
- *Biological Studies:* Mechanisms of oncothermia, thermal-or non-temperature dependent effects, response on electric fields, bioelectromagnetic applications for tumors, Oncothermia treatment combination with other modalities, effects on normal and malignant cells and tissues, immunological effects, physiological effects, etc.
- *Techniques of oncothermia*: Technical development, new technical solutions, proposals.
- Hypotheses, suggestions, opinions to improve the oncothermia and electro-cancer-therapy methods, intending the development of the treatments.

Further information about the Journal, including links to the online sample copies and content pages can be found on the website of the journal: www.Oncothermia-Journal.com.

1. Selbstverständnis und Ziele

Das Oncothermia Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das Oncothermia Journal ist neuen Inhalten gegenüber offen, sollte aber vor allem Studienarbeiten, Fallstudien, Hypothesen, Meinungen und alle weiteren informativen Materialien, die für die internationale Oncotherm-Gemeinschaft hilfreich sein könnten, enthalten. Werbung mit Bezug zum Thema ist ebenfalls willkommen.

- *Klinische Studien*, regionale, lokale oder multilokale Oncothermie oder Electro Cancer Therapy (ECT) Behandlungen, Fallstudien, praktische Erfahrungen in komplexen Behandlungen, klinische Versuche, physiologische Effekte, Oncothermie in Kombination mit anderen Modalitäten und Behandlungsoptimierungen.
- *Biologische Studien.* Mechanismen der Oncothermie, thermale oder temeperaturunabhängige Effekte, Ansprechen auf elektrisches Feld, bioelektromagnetische Anwendugen bei Tumoren, Kombination von Oncothermie und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologsche Effekte etc.
- *Oncothermie*-Techniken. Technische Entwicklungen, neue technische Lösungen.
- Hypothesen, Meinungen, wie die Oncothermie- und ECT-Methoden verbessert werden können, um die Behandlung zu unterstützen.

2. Submission of Manuscripts

All submissions should be made online at the Oncothermia Journal by email Oncothermia-Journal@oncotherm.org.

2. Manuskripte einreichen

Manuskripte können online eingereicht werden: Oncothermia-journal@oncotherm.org

3. Preparation of Manuscripts

Manuscripts must be written in English, but other languages can be accepted by special reasons, when it has an English abstract.

Texts should be supplied in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be supplied in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be supplied in JPG format.

Manuscripts may be any length, but must include:

- *Title Page.* Title of the paper, authors and their affiliations, 1-5 keywords. At least one corresponding author should be identified, whose email address has to be provided with full contact details.
- *Abstracts.* Abstracts should include the: Purpose, Materials and Methods, Results, Conclusions.
- *Test.* Unlimited volume.
- *Tables and Figures.* Tables and figures should be referred to in the text. (numbered figures and tables). Each table and/or figure must have a legend that explains its purpose without reference to the text. Figure files will ideally be supplied as jpg-file (300dpi for photos).
- *References.* Oncothermia Journal uses the Vancouver (Author-Number) system to indicate references in the text, tables and legends, e.g. [1], [1-3], [1-3]. The full references should be listed numerically in order of appearance, and presented following the text of the manuscript.

3. Manuskripte vorbereiten

Manuskripte müssen in englischer Sprache vorliegen. Andere Sprachen können in Ausnahmefällen akzeptiert werden, wenn ein englisches Abstract vorliegt.

Texte sollten in einem mit Microsoft Word für Windows (PC) kompatiblen Format eingereicht werden. Tabellen sollten in einem Word-kompatiblen Format eingefügt werden. Alle Graphiken (Illustrationen, Diagramme, Photographien) sollten im jpg Format vorliegen.

Manuskripte können jede Längen haben, müssen aber die folgenden Punkte enthalten:

- *Titelseite.* Titel der Arbeit, Autor, Klinikzugehörigkeit, 1-5 Schlüsselworte. Es muss mindestens ein Autor ausgewiesen sein, dessen Email-Adresse und Kontaktdetails angegeben werden.
- *Abstracts.* Abstracts müssen enthalten: Zielsetzung, Material und Methoden, Ergebnisse, Fazit.
- *Text.* Beliebige Länge.
- *Abbildungen und Tabellen.* Abbildungen und Tabellen sollten im Text erläutert werden (nummeriert). Jede Abbildung / Tabelle muss eine erklärende Bildunterschrift haben. Bilder sollten als jpg verwendet werden (300 dpi).
- *Zitate.* Das Oncothermia Journal verwendet die Vancouver Methode (Autornummer), um Zitate auszuweisen, z.B. [1], [1-3], [1-3]. Die Bibliographie erfolgt numerisch in Reihenfolge der Erwähnung im Text.

4. Copyright
It is a condition of publication that authors assign copyright or license the publication rights in their articles, including abstracts to the Journal. The transmitted rights are not exclusive, the author(s) can use the submitted material without limitations, but Oncothermia Journal also has right to use it.

4. Copyright
Es ist eine Publikationsvoraussetzung, dass die Autoren die Erlaubnis zur Publikation ihres eingereichten Artikels und des dazugehörigen Abstracts unterschreiben. Die überschriebenen Rechte sind nicht exklusiv, der Autor kann das eingereichte Material ohne Limitation nutzen.

5. Electronic Proofs
When proofs are ready, corresponding authors will receive e-mail notification. Hard copies of proofs will not be mailed. To avoid delays in publication, corrections to proofs must be returned within 48 hours, by electronic transmittal or fax.

5. Elektronische Korrekturfahne
Wenn die Korrekturfahnen fertig gestellt sind, werden die Autoren per Email informiert. Gedruckte Kopien werden nicht per Post versandt. Um Verzögerungen in der Produktion zu verhinden, müssen die korrigierten Texte innerhalb von 48 Stunden per Email oder Fax zurückgesandt werden.

6. Offprints and Reprints
Author(s) will have the opportunity to download the materials in electronic form, and use it for own purposes. Offprints or reprints from Oncothermia Journal are not available.

6. Sonderdrucke und Nachdrucke
Die Autoren haben die Möglichkeit, das Material in elektronischer Form herunterzuladen, Sonderdrucke und Nachdrucke des Oncothermia Journals sind nicht erhältlich.

7. Advertising
The Oncothermia Journal accepts advertising in any languages, but prefers English at least partly. The advertising must have connection with the scope of the Oncothermia Journal and must be legally correct, having controlled values and true info.

7. Werbung
Das Oncothermia Journal akzeptiert Werbeanzeigen in allen Sprachen, wünscht aber die zumindest teilweise Gestaltung in englischer Sprache. Die Werbung muss eine Beziehung zu den Themen des Oncothermia Journals haben und der Wahrheit entsprechende Inhalte aufweisen.

8. Legal responsibility
Authors of any publications in the Oncothermia Journal are fully responsible for the material which is published. The Oncothermia Journal has no responsibility for legal conflicts due to any actual publications. The Editorial Board has the right to reject any publications if its validity is not enough controlled or the Board is not convinced by the Authors.

8. Haftung
Die Autoren aller im Oncothermia Journal veröffentlichten Artikel sind in vollem Umfang für ihre Texte verantwortlich. Das Oncothermia Journal übernimmt keinerlei Haftung für die Artikel der Autoren. Der redaktionelle Beirat hat das Recht,, Artikel abzulehnen.

9. Reviewing
The Oncothermia Journal has a special peer-review process, represented by the Editorial Board members and specialists, to whom they are connected. To avoid personal conflicts the opinion of Reviewer will not be signed, her/his name will be handled confidentially. Papers which are not connected to the scope of the Journal could be rejected without reviewing.

9. Bewertung
Die Texte für das Oncothermia Journal werden vom redaktionellen Beirat kontrolliert. Um Konflikte zu vermeiden, werden die Namen des jeweiligen Korrektors nicht öffentlich genannt. Artikel, die nicht zu den Themen des Journals passen, können abgelehnt werden.

Contents

CONTENTS

The 32nd Annual Conference of the International Clinical Hyperthermia Society (ICHS)

Specialist Papers

Oncothermia Journal 10:15-27 (2014)

The Orientation, Application and Efficacy Evaluation of Hyperthermia in Integrative Natural Therapies of Cancer

Clifford L.K. Pang, Professor, MD, PhD[1]
(1) President (2013) of ICHS, President of WFCMS-SCNT, President of Clifford Hospital

The Orientation, Application and Efficacy Evaluation of hyperthermia in Integrative Natural Therapies of Cancer

Abstract

This report introduces the overview and main mechanism of hyperthermia and summarizes the clinical application of hyperthermia in integrative natural therapies of cancer. According to the clinical experiences of the author, through statistical analysis, this report explains the orientation, application, and efficacy evaluation of hyperthermia in integrative natural therapies of cancer, as well as the understanding of the author.

Key Words

Hyperthermia, Orientation, Application, Integrative Natural Therapies of Cancer, Efficacy Evaluation

Introduction

Hyperthermia, Orientation, Application, Integrative Natural Therapies of Cancer, Efficacy Evaluation

China is one of the earliest countries applying hyperthermia for disease control and treatment. Up to now, hyperthermia and its integrative treatment techniques have been widely applied clinically and have become the fifth main systemic therapy means after surgery, chemotherapy, radiotherapy, and biotherapy. Hyperthermia has thorough and significant lethal effects on cancer and has synergistic effects when integrated with multiple cancer treatments. Modern medicine emphasizes patient-oriented treatment and strives for non-toxic, safe, and reliable therapies. Integrative natural therapies of cancer have unique advantages and curative effects [1]. Hyperthermia has not only inherited the characteristics and advantages of traditional natural therapies, but has also contributed great anticancer effects in combination with modern non-toxic integrative cancer treatments, such as chelation and detoxification therapy, medical ozone therapy, cyto-biological therapy [2].

Based on the significant effect of hyperthermia in the treatment and prevention of cancer, and according to my clinical practice experiences, this report introduces an overview, the main mechanism, the clinical application, integrative natural therapies, and clinical research data of hyperthermia, and presents the orientation, application and efficacy evaluation of hyperthermia in integrative natural therapies of cancer.

1. Overview

Hyperthermia is one of the physiotherapies that use various thermal sources to spread heat throughout an organism for therapeutic purposes. In traditional medicine, hyperthermia is an external therapy of Chinese medicine and includes the use of stone needles, burning acupuncture, medical fumigation, medicated bath, hot wax therapy, moxibustion, etc. In modem medicine, hyperthermia makes use of not only various media to transfer heat to the organism through transmission modes, such as conduction, convection, and radiation, but also the electromagnetism principle, which states that an organism can absorb energy from the electromagnetic field and convert it into thermal energy. Hyperthermia in oncology is a technology and an approach by which the biological tissues are heated to exterminate cancer cells through physical methods.

Making use of the characteristics of the tumor tissue itself, such as distemperedness, slower thermolysis than that of normal tissues during heating, and sensitivity of malignant tumor cells to hyperpyrexia, hyperthermia generates hyperpyrexia through such modes as high-frequency diathermy, radiant heat, and conductive heat, thus killing tumor cells or letting them die out gradually, while normal tissues remain intact.

2. Orientation

2.1. Indications

Indications of hyperthermia include: ①Primary cancer, metastases, recurrent cancer, subclinical lesions, pleural and ascetic fluid, cancer pain, synergistic effects of radiotherapy and chemotherapy, et al. ②Degression of immunity, chronic fatigue or pain, chronic inflammation, all kinds of primary immunologically mediated disease (such as asthma, chronic bronchitis, arthritis, et al.), local tissue edema, local tissue hypofunction, local pain, muscular spasm, regional circulation hypofunction, endocrine system hypofunction, chronic and refractory wounds, recovery phase of injury, insomnia, and health maintenance of genital system or other organs and tissues.

2.2. Clinical Applicable Stage

Hyperthermia is used through the entire treatment process, which fits for all stages and types of patients with wide application. Hyperthermia can lower the rate of infection and other complications, raise resection rate, kill cancer cells, prevent recurrence, eliminate residual disease, exfoliative cancer cells, contribute synergistic effects for radiotherapy and chemotherapy, et al., when it is used during surgery. Hyperthermia is also used on post-treatment patients with recurrence or drug resistance. It can raise the tolerance and compliance of patients, guaranteeing the continuity and integrity of the therapeutic regimen.

Hyperthermia's integration with therapies of Traditional Chinese Medicine such as Chinese medicine, acupuncture, massage moxibustion, and medical Qigong, is of great innovation in cancer treatment. It also eases the treatment process, by improving immune function and preventing the complications and adverse effects of radiotherapy and chemotherapy.

2.3. Application of Hyperthermia in Integrative Natural Therapies of Cancer

The connotation, connection, and application of hyperthermia in oncology and natural therapies are expatiated in my book Hyperthermia in Oncology, so I won't spend more time for explanation at this time. Cancer is a kind of whole body disease. Anti-cancer treatments should not just target cancer lesions, and one single therapy for cancer cannot have ideal effects in the clinic. Through clinical practice, integrative cancer treatments have gradually changed from the original passive therapies to predictable ones, especially when the "integrated treatments" concept, "treatments for triple factors (the patient, place and time)," and "patient-oriented" principle of TCM have been introduced into modem cancer therapies. The theory emphasizes mostly improvement of organism functions and stabilization of internal environment. It focuses on controlling both primary cancer and micrometastases, curing in combination with preventing, and prolonging survival time based on the quality of life. Hyperthermia's addition to integrative cancer treatments, as a "non-toxic treatment," has made a great change in the old theory of simply killing cancer cells, emphasizing both killing cancer cells and activating the internal ability of the human body to prevent or treat cancer by improving the immune system.

Hyperthermia inherits two principles of traditional natural therapy: patient-orientation and strengthening of the body's resistance to encourage elimination of pathogens. It develops from natural therapy and originates with TCM. Hyperthermia also blends well with modern treatments. In the development of non-toxic integrative cancer treatments, hyperthermia takes over from the

past and sets a new course for the future, thoroughly cooperating with various cancer treatments with synergistic effect. With great cohesion, it plays an important role in modern and non-toxic integrative cancer treatments.

3. Clinical Application

3.1. Hyperthermia Combined with Surgery

Surgery is a preferred therapy for various tumors. It plays an important therapeutic role. Hyperthermia can destroy tumor blood vessels and depress the invasion and metastasis of tumors, [3], [4], [5]. It can damage the microcirculation of tumor tissues and result in the necrosis of tumors. Hyperthermia strengthens the functions of immune cells and controls the growth and restoration of tumor cells [6]. At the same time, hyperthermia generates heat shock protein through heat stress and causes immune response that kills tumor cells. With the ability to restrain cell reproduction of cancer cells, damage the normal functions of cell membranes, restrict the respiration of cancer cells, and strengthen lysosomal activity, hyperthermia can kill cancer cells directly, [7], [8].

The adjunctive therapies with hyperthermia in sugery include: ① preoperative hyperthermia: preoperative single hyperthermia, preoperative hyperthermic chemotherapy, preoperative hyperthemal perfusion, preoperative hyperthermia combining radiotherapy and chemotherapy, etc,; ② intraoperative hyperthermia: focusing on regional hyperthermia, common intraperitoneal chemo hyperthermia, intraoperative electrotome burning foci, etc.; ③ postoperative hyperthermia: for any patient who does not require radiotherapy or chemotherapy, single hyperthermia combined with other comprehensive therapies can be applied to prevent any reoccurrence or metastasis.

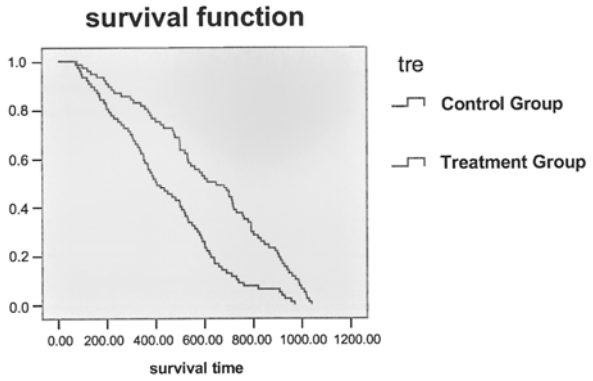
3.2. Hyperthermia Combined with Chemotherapy

Hyperthermia has synergistic effects when combined with chemotherapy [9]. Chemotherapy can be combined with local hyperthermia or whole body hyperthermia. Each deep radiofrequency hyperthermia lasts for an hour, once every 2~3 days. Each whole body hyperthermia lasts for 6-8 hours, with its therapeutic temperature maintained at 39.5~41.8·^{o}C for 180 minutes at the minimum, once every 10~14 days. If local hyperthermia is combined with whole body hyperthermia, it can be conducted in the interval between two treatments of whole body hyperthermia. If chemotherapy is combined with local hyperthermia, the local hyperthermia can be conducted after the therapeutic drug administration. If chemotherapy is combined with whole body hyperthermia, the chemotherapeutic drug can be infused during whole-body hyperthermia which is conducted on the first drug administration of each chemotherapy period. A local hyperthermia can be conducted every other day in the interval between two chemotherapies. During the therapy, routine allopathic supporting therapies are conducted to prevent and cure any adverse reactions. Intracavitary chemotherapy is mostly combined with local hyperthermia and includes intraperitoneal hyperthermic chemo perfusion, intrapleural hyperthermic chemo perfusion, and intravesical hyperthermic chemo perfusion.

154 patients diagnosed with epithelial ovarian cancer metastases in the abdominal cavity were randomly divided into 2 groups (Treatment Group and Control Group). The Treatment Group (consisting of 77 patients) was treated by RF local thermotherapy in combination with IHCP. The Control Group (consisting of 77 patients) was treated by normal chemotherapy trough intravenous injection. Both groups were followed up for 2 years. The tumor control rate, decrease in tumor markers, improvement in quality of life, and extension of survival time in Treatment Group was superior to Control Group (Table 1, Chart 1).

	Tumor Controlling Rate	CA125 decrease >50%	Controlling Rate of Pain	KPS Increase >10 分	progression free-time>1 year
Treatment Group	87.0%	43 cases	73.5%	52 cases	40 cases
Control Group	64.9%	26 cases	36.5%	31 cases	25 cases
	P<0.01	P<0.01	P<0.01	P<0.01	P<0.01

Table 1. Research Results of RF Local Thermotherapy in Combination with IHCP



Integer Comparison

	卡方	df	Sia.
Log Rank (Mantel-Cox)	21.574	1	.000
Breslow (Generalized Wilcoxon)	17.442	1	.000
Tarone-Ware	19.863	1	.000

Tre of different level test of survival distribution equivalence

Chart 1. Survival Curves of 2 Groups

In another research study, 156 patients who finished 1 course of Local hyperthermia and a 3-month follow-up were selected as a Treatment Group. The tumor types of the patients are as follows (Chart 2).

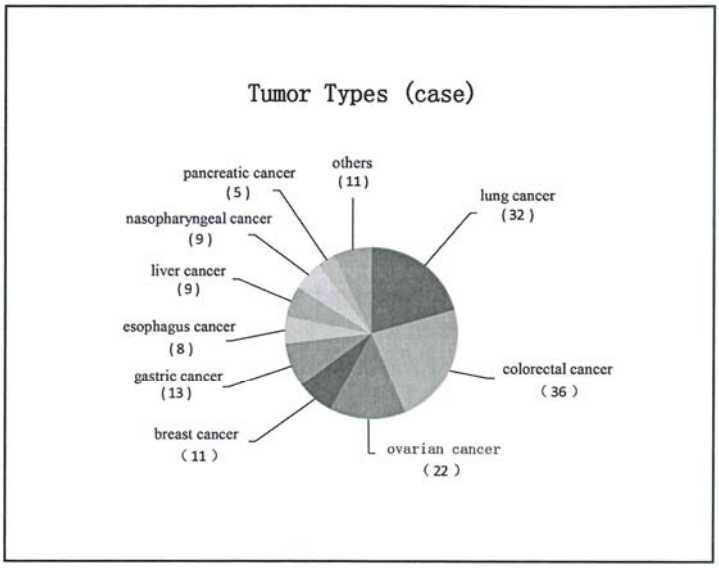


Chart 2. Tumor types

Others included renal carcinoma, osteosarcoma, lymphoma, cervical cancer, rhabdomyosarcoma, and tongue cancer. All patients were diagnosed by pathologic and imaging diagnosis combined with clinical definitions according to the cancer diagnostic criteria of WHO (World Health Organization). They were at Stage III/IV or with recurrence after surgery (Table 2). Meanwhile,

another 150 cases were selected randomly from the patients with advanced tumors who didn't receive hyperthermia at the same period in hospital (Table 3). They were observed as the Control Group. After follow-up and observation, the effectiveness of the therapies of Treatment Group is superior to those of Control Group. The therapeutic regimens of both groups are as follows (Table 2, 3 and 4).

Treatments	Cases	CR	PR	NR	Effective Power
Local hyperthermia	75	5	43	20	64.0%
Local hyperthermia + Whole Body Chemotherapy	14	2	9	4	78.6%
Local hyperthermia + Intraperitoneal Hyperthermic Chemo Perfusion	42	3	23	11	61.9%
Local hyperthermia + Intravesical Hyperthermic Chemo Perfusion	13	1	7	4	61.5%
Local hyperthermia + Radiotherapy	12	1	8	2	75.0%
Total	**156**	**13**	**90**	**41**	**66.0%**

Table 2. Therapeutic Effect of 156 Patients in Treatment Group

Treatments	Cases	CR	PR	NR	Effective Power
Whole Body Chemotherapy	51	4	31	8	68.6%
Intraperitoneal Hyperthermic Chemo Perfusion	45	1	18	11	42.2%
Intravesical Hyperthermic Chemo Perfusion	24	0	12	3	50.0%
Radiotherapy	30	1	15	5	53.3%
Total	**150**	**6**	**76**	**27**	**54.7%**

Table 3. Therapeutic Effect of 150 Patients in Control Group

	Treatment Group	Control Group	x^2	P
Cases	156	150		
CR+PR	103	82	4.13	0.01<P<0.05
Effective Power	66.0%	54.7%	4.08	0.01<P<0.05

Table 4. Therapeutic Effect Comparison of 2 Groups

3.3. Hyperthermia Combined with Radiotherapy

Hyperthermia has synergistic effects when combined with radiotherapy [10], [11], [12]. For patients targeted with radiotherapy indication or those without hyperthermia contraindication, radiotherapy and hyperthermia are conducted simultaneously. As for local hyperthermia combined with radiotherapy, the local hyperthermia is conducted every other day after the radiotherapy. As for whole body hyperthermia combined with radiotherapy, whole body hyperthermia is conducted once every 10~14 days after radiotherapy. During the period between two treatments of whole body hyperthermia, local hyperthermia is conducted every other day, also right after radiotherapy. During the therapy, routine allopathic supporting therapies are conducted to prevent and mitigate any adverse reaction.

Wu Jingbo [13] et al. have implemented controlled clinical studies on cavity microwave hyperthermia combined with emission treatment, and the results have shown that the thermoradiotherapy group had a higher rate of CR compared with the single radiotherapy group. Liu Shixi [14], et al. have reported that with the implementation of hyperthermia when conducting the conventional irradiation DT40Gy, the rate and extent of tumor regression in the thermoradiotherapy group were superior to the single radiotherapy group. Clinical studies of Margin, RL [15], et al. have shown that combination with local hyperthermia can improve local efficacy of radiotherapy. Studies of Manning, MK [16], et al. also have confirmed that single microwave hyperthermia could not only have anti-tumor effects, but could also increase the sensitivity of tumor cells to radiation. Combination treatment of nasopharyngeal carcinoma and cervical lymph node metastasis had significant effect.

3.4. Hyperthermia Combined with TCM Therapies

Hyperthermia combined with TCM therapies shows typical characteristics of natural therapy. It expresses the principles of non-toxic integrative cancer treatments which I have been practicing and making successful progression.

3.4.1. Hyperthermia Combined with Orally-taken Chinese Medicine

According to the tumor symptoms of Qi stagnation, blood stasis, abdominal mass, and cold stagnation, TCM is applied to drive out cancer toxins and regulate immunity, and it can be combined with cancer hyperthermia. Each local hyperthermia lasts for an hour, 5~10 treatments every 2~3 days. Whole body hyperthermia lasts for 6~8 hours with its therapeutic temperature maintained at 39.5~41.8 ^{0}C for no less than 180 minutes, once every 10 ~ 14 days. If the local hyperthermia is combined with whole body hyperthermia, it can be conducted every other day in the interval between two treatments of whole body hyperthermia. TCM taken orally is used for treatment based on syndrome differentiation in accordance with the specific conditions of a patient, one dose a day to be divided for consumption in morning and evening. Due to the restriction on eating and drinking the day before whole body hyperthermia, a dose of TCM should be strongly decocted and taken orally after the completion of whole body hyperthermia.
In one research study of mine, 157 patients with colorectal cancer in Clifford Hospital from May, 2005, to June, 2008, were divided randomly into 3 groups [17], (Table 5).

Groups	Patients	Therapeutic Regimens
Treatment Group	53	Local hyperthermia + Clifford Guben Xiaoliu Decoction (Chinese medicine, taken orally)
Control Group A	50	Local hyperthermia
Control Group B	54	Clifford Guben Xiaoliu Decoction (Chinese medicine, taken orally)

Table 5. Therapeutic Regiments of 3 Groups

All patients were followed up for 2 years. Comparing the therapeutic effect, improvement in quality of life, and survival time of the 3 groups, the results for Treatment Group were superior to both Control Group A and B.

Groups	CR+PR+NC	KPS	VAS	Survival Time
Treatment Group	42	71.67 ± 30.36	3.755 ± 2.841	709.47 ± 14.21
Control Group A	31	50.68 ± 36.44	5.22 ± 3.00	661.18 ± 21.14
Control Group B	28	53.76 ± 37.60	4.80 ± 2.77	662.64 ± 20.03
P	<0.05	<0.05	<0.05	<0.05

Table 6. Results of 3 Groups

In the researchers of Ge Guoxin [18], Chen Liwei [19], et al. on Local hyperthermia combined with orally-taken Chinese medicine, the progression of tumors was well controlled with improvement in quality of life, extension of survival time, increase of survival rate, and decrease of tumor markers. No adverse reaction was observed, and the result was superior to routine chemotherapy.

3.4.2. Hyperthermia Combined with Chinese Medicine Infused in Body Cavity and Lumens

TCM directly touching or close to the diseased region is combined with deep heating to increase the therapeutic effect, once per 2- 3 days, for one hour each time, with 10 times as a course of treatment. It is applied to various tumors, of which colon cancer (descending colon cancer, sigmoid colon cancer, and rectal cancer) and prostatic cancer are the easiest to administer using TCM.

Some researchers used Rabdosia liquid for intravesical hyperthermic perfusion on patients with bladder cancer. After treatments, the increase of CD4+ and CD4+/CD8+ and the decrease of SIL-2R implied that the immune functions of patients was improved. Li Dengbao [20], et al. conducted research on 28 patients with bladder cancer. After surgeries, Rabdosia liquid intravesical hyperthermic perfusion was given. The changes of T lymphocyte subsets and SIL-2R in serum were recorded and compared with healthy people in the control group. As a result, the immune functions of these patients were improved.

3.4.3. Hyperthermia Combined with External Application of Chinese Medicine

External application is a main method of TCM. It adopts easily through skin administration and attains the healing purpose through drug potency which is infiltrated into the local area. It is then transferred throughout the viscera to dredge Qi movement and strengthen vital Qi so as to dispel pathogenic factors. The means of absorption approaches of these drugs through the skin mainly include: arterial passage, hydration, surfactant effect, and auxoaction of the aromatic drugs. How to improve the permeability of drugs through the skin is a key to obvious therapeutic effects. The epidermis must be softened to accelerate drug infiltration, and heat stimulation of the skin surface is an effective means for softening the epidermis.

Method: Herbal drugs are prescribed for treatment based on syndrome differentiation. Then the drugs are powdered and mixed with alcohol, vinegar, or honey to form a paste, which is applied to the surface of the pathological areas with dressing. External application is conducted after deep or whole-body hyperthermia.

Local hyperthermia lasts for an hour each time, once every 2~3 days, with 10~15 times as a course. Whole body hyperthermia lasts for 6~8 hours each time with the therapeutic temperature maintained at 39.5~41.8 ^{o}C for 180 minutes at the minimum, once every 10~14 days. If Local hyperthermia is combined with whole body hyperthermia, it can be conducted every other day in the interval between two treatments of whole-body hyperthermia. Herbal drugs are powdered and packed into specially-made vests and bellybands to wrap around the patient, and then medium and low temperature hyperthermia is conducted, once a week, for 2~3 hours each time, at a temperature of 38~40 ^{o}C, with five times as a course. It is mainly used for benign diseases.

Mo Dingqun [21], et al. consider that microwaves can destroy the stability of the cellular membrane and promote the penetration and absorption of herbs. Besides, microwave hyperthermia can strengthen the activity of herbs and significantly raise therapeutic effects. In their clinical practice, microwave hyperthermia combined with external application of Chinese medicine to treat cancer pain in the liver area of 20 patients with liver cancer; 11 patients were totally relieved from pain, and 9 patients were able to reduce their dose of pain killer.

The therapeutic effect was observed in all patients.

3.4.4. Hyperthermia Combined with TCM Technologies (Acupunture, Moxibustion, Massage, Cupping Therapy, Bee Venom Therapy, Auricular Point, etc.)

During anticancer therapy, TCM technologies, such as acupuncture, moxibustion, massage, cupping therapy, bee venom therapy, and auricular point, can strengthen the vital Qi to eliminate pathological factors, strengthen immunity, regulate the energy balance of the human body, improve the functions of the organism, and so on. TCM technologies are especially characterized by simplicity, convenience, cheapness, efficacy without side effects or toxicities, and are real "green therapies". Both single and combined applications play important roles during cancer therapies.

3.4.5. Hyperthermia Combined with Medical Qigong

Medical Qigong has been practiced for over a thousand year. Medical Qigong is a non-medicated health-building therapy through the physiological and psychological processes of exercises such as

regulating the body, breathing and mental activities, relaxing limbs, adjusting respiration, and stabilizing spirit consciousness, etc, so as to regulate the balance of Yin and Yang in the human body. The combination of hyperthermia with medical Qigong is an innovation in the field of tumor therapy, which is beneficial to the improvement of symptoms and long-term therapy on tumors.

3.5. Hyperthermia Combined with Integrative Natural Therapies of Cancer

Cancer treatments should be whole-person oriented and focus on entirety and individuality, which require integrative treatments. According to clinical observations and summaries in integrative natural therapies, hyperthermia plays an important part in controlling tumors, relieving symptoms, improving quality of life and so on. Besides hyperthermia, non-toxic integrative cancer treatments also include medical ozone, chelation therapy, enema therapy, systemic biofeedback therapy, nutritional therapy, Chinese herbal medicine diet, medical Qigong, cell therapy, constitutional alkalinization therapy, TCM, etc. We have observed 210 patients with Stage IV cancer in Clifford Hospital (Chart 3), and studied the different effects of non-toxic integrative cancer treatments, simple integrative natural therapies and routine anticancer and allopathic supporting therapies on control rate of tumor, symptoms, and quality of life.

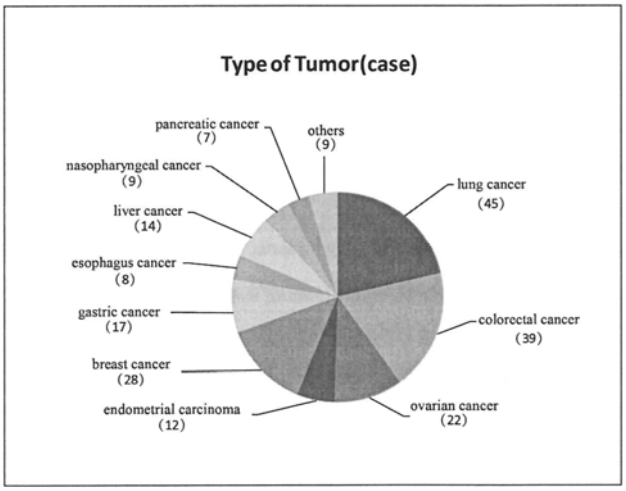


Chart 3. Tumor Types

Other tumors include renal carcinoma, lymphoma, cervical cancer, etc. Patients were divided into 3 groups randomly: Group A received non-toxic integrative cancer treatments with hyperthermia as the main treatment. Group B received simple integrative natural therapies. Group C received routine anticancer therapies (radiotherapy, chemotherapy, targeted therapy, etc.) and allopathic supporting therapy. The therapeutic regimen of non-toxic integrative cancer treatments in Group A were formulated by a group of oncology experts in Clifford Hospital according to the body condition and clinical examination results of patients. Evaluation of symptomatic relief: the feelings of nausea, bad appetite, fatigue, dizziness, abdominal distension, chest distress, and fever are relieved, and the decrement of drug dosage for allopathic supporting therapy is more than 50%. Evaluation of pain control: Excellence: Without pain after treatments of the dose of pain killers reduced to 1/3 of the dose before treatments. Utility: The dose of pain killers reduced to 1/3~2/3 of the dose before treatments. Nullity: No relief of pain, or tiny relief, but the necessary dose of pain killers is still more than 2/3 of before. The required time of excellence or utility evaluation should last more than 3 days. Evaluation of performance status is based on the Karnofsky Performance Status (KPS). Significant improvement: KPS increases more than 20 points after treatments. Improvement: KPS increases 10~19 points after treatments. No Improvement: KPS increases less than 10 points after treatments. After 4 courses of treatments, therapeutic results were as follows (Table 7, 8, 9 and 10):

3.5.1. Tumor Control of 3 Groups

	CR	PR	NC	PD	Rate of Tumor control (CR+PR+NC)
Group A	3	24	25	18	74.3%
Group B	1	17	22	30	57.1%▲
Group C	0	12	17	41	41.4%••*

Table 7. Tumor Control of 3 Groups

3.5.2. Symptomatic Relief of 3 Groups

	Total Cases	Cases with Symptomatic Relief	Rate of Symptomatic Relief
Group A	70	54	77.1%
Group B	70	43	61.4%▲
Group C	70	26	37.1%••**

*A&B: ▲P<0.05, ▲▲P<0.01; A&C: •P<0.05, ••P<0.01; B&C: *P<0.05, **P<0.01*

Table 8. Symptomatic Relief of 3 Groups

3.5.3. Pain Control of 3 Groups

	Cases with Pain	Excellence	Utility	Nullity
Group A	49	13	26	10
Group B	52	9	15	28
Group C	48	3	8	37

Table 9. Pain Control of 3 Groups

After treatments, pain control rates were compared between Group A and B, A and C, B and C trough $\chi 2$ test, and there were significant differences ($P<0.05$). The control rate of Group A was superior to Group B and C. The control rate of Group B was superior to Group C.

3.5.4. Performance Status of 3 Groups

	Total Cases	Significant Improvement	Improvement	No Improvement
Group A	70	10	39	21
Group B	70	5	22	43
Group C	70	1	13	56

Table 10. Performance Status of 3 Groups

After treatment, performance status were compared between Group A and B, A and C, B and C trough x2 test, and there were significant differences ($P<0.05$). The performance status of Group A was superior to Group Band C. The control rate of Group B was superior to Group C. This research indicated that non-toxic integrative cancer treatments with hyperthermia as the main treatment were superior to simple integrative natural therapies for tumor control, symptom relief, and improvement of quality of life, and were superior to routine anticancer therapies (radiotherapy, chemotherapy, targeted therapy, etc.) and allopathic supporting therapy for these applications as well while treating patients with advanced cancer.

Besides, through clinical observation of patients with advanced cancer, hyperthermia combined with chelation therapy were significantly superior for symptom relief and improvement of quality of life.

I have observed 57 patients with advanced cancer in 2009-2011. The patients received hyperthermia combined with chelation and detoxification therapy, with allopathic supporting therapy. Compared with another 62 patients who received palliative therapy, hyperthermia combined with chelation and detoxification therapy was significantly superior on symptom relief and improvement in quality of life. Satoh [22], et al. discovered that during the process of

hyperthermia, the degradation of vitamin C and vitamin C-sodium hydride was strengthened, and generated more free radicals of vitamin C. The increase of free radicals strengthened the anticancer effect of hyperthermia, which explained why hyperthermia combined with vitamin C had stronger anticancer effects. Hyperthermia can also be combined with physical therapies such as recovery therapy, external application therapy, cryotherapy, electrotherapy and electromagnetic therapy. Each combination will improve therapeutic effects on malignant diseases and their complications, such as cancer pain.

In summary, I have practiced hyperthermia combined with the therapies above with creativity and exploration. The effects of these combinations are for the purpose of improving the functions of the human body, which is called "strengthening body resistance" in TCM. By increasing permeability of cell membranes, raising drug concentration and reaction speed, increasing oxygen content of the cells around tumors, and starting the antigen antibody systems in the body, hyperthermia combined with these therapies introduced above can improve the self compensation and balancing ability of the human body to inhibit the replication of cancer cells; this is called "strengthening healthy Qi to eliminate pathogens" in TCM. Additive or synergistic effects have been obtained in the practice of integrative therapies, which is a creative work. Hyperthermia's integration into modern medicine still requires further research.

4. Efficacy Evaluation and Analysis

According to the therapeutic effect evaluation criterion of the World Health Organization (WHO), through my studies and practices, hyperthermia combined with palliative routine anticancer therapies such as radiotherapy, chemotherapy through intravenous injection, and intracavitary chemotherapy approached the rate of 60% of tumor control in both randomized controlled study and concurrent control study, and was superior to routine anticancer therapies and allopathic supporting therapy, with statistical significance. When combined with integrative natural therapies, especially TCM, hyperthermia not only shows unique therapeutic effects, but also provides new ideas and methods to patients with recurrence, metastases, or drug resistance. It brings a new hope to the patients who have already lost the chance of surgery, radiotherapy or chemotherapy.

In my practices, the effects of improving immune functions, removing the cause of disease, controlling tumor progression, improving quality of life, prolonging survival time, raising survival rate, and decreasing cancer markers without adverse reactions was proved when hyperthermia was combined with integrative natural therapies for cancer on different types of cancer, especially the advanced ones. The rate of tumor control and symptom relief even reached 70% in some research. The advantage is significant in both common treatments and alleviative treatments. Referring to some other reports, hyperthermia combined with integrative natural therapies has consistency with the anticancer therapeutic results of the author. Hyperthermia is an indispensable part of integrative natural therapies for cancer, and makes them more scientific, reasonable, and effective.

Therefore, clinical researches and records prove that hyperthermia is safe and reliable in treating cancer. It inherits the characteristics of traditional natural therapies and can integrate with modern anticancer techniques through development. Hyperthermia can be used at all stages of cancer. It is an irreplaceable part of integrative natural therapies of cancer, as well as a wonderful element of TCM.

5. Conclusion

Our clinical practices have proved that hyperthermia in combination with integrative natural therapies can kill cancer cells by effectively removing the cause of disease, detoxifying human body, and improving immune system and the self-healing capacity of the human body. It obtains the purpose of treating both manifestation and root cause of disease, so as to prolong survival time of patients and improve the quality of life.

6. Prospect

In my opinion, based on the systematic principle of “nature-human integration", with the transformation of the medical model from biomedical model to bio-psycho-social medical model, tumor therapy is no longer a single treatment for diseases, but is the best mode which stresses participation of a variety of means and disciplines and is patient-oriented. It not only focuses on tumor control and prolonging survival, but also pays more attention to the patient's overall quality of life by adopting measures suitable to the patient, place, and time. It emphasizes a combination of treatment methods customized for the patient and strives to obtain comprehensiveness of diagnosis and treatment of tumor diseases. Non-toxic integrative cancer treatment with hyperthermia as a main part has become the trend and advantage in cancer treatment development.
I have achieved gratifying results after clinical practice by combining hyperthermia with conventional cancer treatments and have put forward the concept of "Integrated Green Therapy of Tumor." This concept requires physicians to discuss and design optimized antineoplastic protocols based on the disease itself and, with the consideration of the patient's individual genetic background, physical condition, living environment, psychology, and other factors, fully participate in the implementation and revision of treatments to ensure standardization and internationalization of treatments and management. As shown in clinical validations, the combination of different subjects, the mixture of multiple traditional natural therapies, and the practice of modern non-toxic treatments have brought new hope to innumerable cancer patients, especially those with medium to advanced cancers. It embodies dialectics of scientific treatments for cancer and ensures the most appropriate combined therapy in order to achieve the purpose of controlling tumors, extending survival time, and improving the quality of life of the patients.

7. Appendix

Appendix 1: Assessment on Curative Effect

Curative effect is evaluated according to the WHO criteria.

7.1. Evaluation of measurable lesions

Complete Remission (CR): all measurable lesions completely disappear for more than 4 weeks.
Partial Remission (PR): decrease in tumor volume being more than 50% for more than 4 weeks, serum tumor indicators significantly declined with statistical significance.
No Change (NC): increase in tumor volume being less than 25% or decrease less than 50% for more than 4 weeks.
Progress and Development (PD): tumor not able to be controlled and increase in tumor volume being more than 25%, or new lesions present, or blood tumor indicators significantly increased with statistical significance.

7.2. Evaluation of lesions which cannot be measured

Complete Remission (CR): all visible lesions disappeared, and this situation maintained at least for more than 4 weeks.
Partial Remission (PR): decrease in entire tumor estimated to be more than 50%, and this situation maintained for more than 4 weeks.
No Remission (NR): lesion has no significant change at least 6 weeks after treatment, the increase in the tumor estimated to be less than 25%, or the decrease in the tumor estimated to be less than 50%.
Progress and Development (PD): new lesions present, or the increase in original lesions estimated to be more than 50%.

7.3. Evaluation of Quality of Life

Comprehensive evaluation is made according to KPS and VAS scores.

7.3.1. KPS score

Karnofsky (100-point method) Performance Status (Appendix Table 1)

Performance Status	Scores
Normal, no signs and symptoms	100
Capable of normal activities; mild signs and symptoms	90
Barely capable of normal activities; some signs or symptoms	80
Capable of self care; but inability to maintain normal life and work	70
Capable of self care in most cases; but occasionally need help	60
Always need care	50
Incapable of self care; need special care and assistance	40
Incapable of self care to a serious extent in the life	30
Seriously ill; need to be hospitalized and active support treatment	20
Critical illness; close to death	10
Death	0

Appendix Table 1. KPS

7.3.2. Pain Evaluation

VAS (Visual Analogue Scale) pain evaluation: The pain level is represented by 0 to 10, a total of 11 numbers. 0 represents painless, 10 most painful. Patients choose one of these 11 numbers according to their pain level.

Level of Pain	Scores
No pain	0
Mild pain that can be tolerated	<3
Pain that affect sleep but can still be tolerated. The pain should be clinically relieved	4~6
More intense pain that can not be tolerated	7~10

Appendix Table 2. VAS

Regarding the evaluation of integrative natural therapies, the TCM diagnostic performance (collected by look, smell, ask, touch), nutritional assessment, and psychological assessment should be considered as well in the general conditional evaluation of patients. This makes the physical and psychological evaluation more comprehensive. It also helps to make scientific, comprehensive, humanized, and individualized therapeutic regiments with objective and practical efficacy.

Appendix 2: Common Methods of Hyperthermia

Tumor Location	Therapeutic method
Malignant tumors (except brain tumor) without contraindications	Whole-body hyperthermia or whole-body hyperthermia combining other therapies
Depth of superficial tumors < 3 cm	915 MHZ common microwave radiator ultrasound
Depth of superficial tumors < 3 cm	Focused radiator microwave, intraoperative multi-head ultrasound
Brain tumor	Interstitial hyperthermia, extracorporeal deep radiofrequency hyperthermia Ultrasound after craniotomy, low power radiofrequency

Metastasis of nasopharyngeal carcinoma carotid < 3 cm	Intracavitary microwave, ultrasound, extracorporeal deep radiofrequency hyperthermia
Esophagus cancer	Intracavitary microwave, intracavitary radiofrequency, extracorporeal deep radiofrequency hyperthermia
Lung cancer	Whole body hyperthermia, extracorporeal deep radiofrequency hyperthermia
Lung cancer	Intraoperative hyperthermia, extracorporeal deep radiofrequency hyperthermia
Pancreatic cancer, gastric cancer, ovarian cancer	Intraoperative interstitial hyperthermia, endoscopic interstitial and regional hyperthermia Extracorporeal deep radiofrequency hyperthermia
Rectal cancer	Intraoperative hyperthermia, intrapeitoneal chemohyperthermia Extracorporeal deep radiofrequency hyperthermia
Bladder cancer	Intracavitary hyperthermia, regional hyperthermia, hyperthermal perfusion Extracorporeal deep radiofrequency hyperthermia
Uterine neck, cervical cancer	Regional hyperthermia, hyperthermic perfusion, radiofrequency, ultrasound, focused ultrasound
Prostatic cancer	Intracavitary hyperthermia, regional hyperthermia, extracorporeal deep radiofrequency hyperthermia
Limb osteosarcoma	Interstitial heating, regional hyperthermia, extracorporeal deep radiofrequency hyperthermia Intraoperative hyperthermia, isolative perfusion, ring induction heating

Appendix Table 3. Commonly Used Hyperthermia Treatments

References

[1] Clifford L.K. Pang. A Study of Non-Toxic Integrative Cancer Treatments [M]. Beijing: China Press Of Traditional Chinese Medicine, 2008.
[2] Clifford L.K. Pang. Hyperthermia in Oncology [M]. Beijing: People's Medical Publishing House, 2013.
[3] Tang Jintian, Hyperthermic Biology of Cancer [M]. Beijing: People's Medical Publishing House, 2010.
[4] Jia Siyuan, Luo Xiangdong, Qi Jie. Study on thermal stress on proliferation of vascular endothelial cells and its mechanism [J]. Journal of Traumatic Surgery, 2003, 5(3):211-213.
[5] Sawaji Y, Sato T, Takeuchi A, et al. Anti-angiogenic action of hyperthermia by suppressing gene expression and Production of tumor-dericed vascular endothelial growth factor in vivo and in vitro [J]. Br J Cancer, 2002, 86(10):1597
[6] Fang Dingzhu. Progress of tumor local thermotherapy and antitumor immunity [J]. Medical Review, 2007, 13(5): 342-343
[7] Tang Yanxia, Zhang Helong. Progress of research on the mechanism of tumor hyperthermia [J]. Modern Medical Journal, 2008, 16(3): 473-475
[8] Jing Wenhua, Ding Yayuan. Research progress of clinical application of tumor hyperthermia [J]. Nursing Research, 2007, 21(7): 1799-1800
[9] Kahashi I, Emi Y, Hasuda S, et al. Clinical application of hyperthermia combined with anticancer drugs for the treatment of solid tumors. Surgery, 2002, 131(1SuPP1): S78-S84
[10] VanderZee J, Van Rhoon GC. Hyperthermia is effective in improving clinical radiotherapy results [J]. Int J Radiat Oncol Bioi Phys, 2006, 66: 633-634
[11] Arcanmgeli G, Cividall A, Nervi C et al. Tumor Control and therapeutic gain with different schedules of combined radiotherapy and local external hyperthermia in human cancer. Int J Radiat Oncol Biol Phys, 1983, 9:1125
[12] Nishimura Y, Hiraoka M, Mitsumori M, et al. Thermoradiotherapy of superficial and subsurface tumours: analysis of thermal parameters and tumour response [J]. Int J Hyperthermia, 1995, 1:603-613
[13] Wu Jingbo, Chen Chengqin. Clinical Study of intracavitary microwave hyperthermia combined with radiotherapy for nasopharyngeal carcinoma [J]. Sichuan Cancer, 1997, 10(Supplement):12-15
[14] Liu Shixi, Chen Daishu, Zhang Shijie, et al. Study on microwave hyperthermia combined with radiotherapy for nasopharyngeal carcinoma [J]. Journal of Clinical Department of ENT, 1997, 11(4): 150-152
[15] Margin, RL, Peterson AF. Noninvasive microwave phased arrays for local hyperthermia: a review[J]. Int J Hyperthermia, 1989, 5(4): 429-450
[16] Manning MK. Clinical hyperthermia employing hyperthermia alone or in combination with external beam or interstitial radiotherapy[J]. Cancer, 1982,49:205-208
[17] Clifford Pang. Clinical research on integrative treatment of colon carcinoma with oncothermia and Clifford TCM Immune Booster[J]. Oncothermia Journal, 2010, 1: 26
[18] Ge Xinguo, Wang Ying. Clinical study on analgesic powder in the treatment of pancreatic carcinoma with high intensity focused ultrasound hyperthermia [J]. Chinese Journal of Medical Imaging Technology, 2006, 22(8): 1223-1226
[19] Chen Liwei, Wang Yuhan. Research of hyperthermia combined with TCM drugs to improve the quality of life of patients with malignant tumor and immunity [J]. Sichuan Traditional Chinese Medicine, 2004, 24(2): 63-64
[20] Li Dengbao, Zhao Gaoxian, Gu Jiang. Effect of Rabdosia rubescens liquid bladder hyperthermia on subsets of T lymphocytes and SIL-2R inpatients with bladder cancer [J]. Clinical Medicine, 2005, 25(7): 5-7
[21] Mo Dingqun, Wang Xiande, Liu Qiang. Microwave hyperthermia combined with traditional Chinese medicine sticking therapy for pain of liver cancer in 20 cases [J]. Chinese Folk Medicine, 2001, 9(11): 42
[22] Satoh K, Sakagami H, Nakamura K. Enhancement of radical intensity and cytotoxic activity of ascorbate by hyperthermia[J].Anticancer Res.1996, 16(5A):2987 -91

Oncothermia Journal 10:29-31 (2014)

Relation between Compliance and Response-Recurrence Rates in Head and Neck Tumors Treated with Hyperfractionated Thermo radiotherapy

Haim I. Bicher, M.D.[1]

(1) Bicher Cancer Institute – 12099, W. Washington Blvd., #304 Los Angeles – Ca. 90066 - USA

Relation between Compliance and Response-Recurrence Rates in Head and Neck Tumors Treated with Hyperfractionated Thermo radiotherapy

Introduction

Hyperthermia, applied regionally, is a potent sensitizer of radiation therapy in the treatment of cancerous tumors and as such has been used as a palliation measure or more recently with curative intent. The ability of Hyperthermia to reoxygenate tumor tissue makes hypoxic tumors, such as sarcomas or glioblastomas more responsive to radiation. In a prior publication we discussed good therapeutic results (over 80% 5 years survival) using Hyperfractionated Thermoradiotherapy (HTRT) in heatable superficial tumors. In the current investigation we report on an expanded series of patients as well as performing a meta-analysis comparing HTRT with external beam radiation (EBRT) or chemoradiation.

Material and Methods

Hyperthermia was delivered using either Microwaves (BSD-100 or Cheng Laboratories) or Ultrasound (Labthermics) FDA approved equipment with appropriate applicators. Thermometry was done using microthermocouples placed in the tumor region (BCIW, LA, CA) for prostate tumors only ultrasound was used. Radiation was delivered by a 12 MEV Siemens Mevatron Machine adapted for IMRT and IGRT with a Lina-Tech system for computer planning and collimator alteration. Fractionation used involved daily hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180cGy to 100cGy resulting in the isoeffect biological equivalent dose lower by 15% to 25%, according to Ellis TDF formula. This decrease is compensated by the increased number of hyperthermia fractions which potentiates each radiation dose. Treatment is continued until an objective complete response is adained, or failure determined. 40 breast patients, 27 head and neck and 22 prostate patients were treated with a follow-up of two to five years. All patients were early stage (III-a or less) the total dose is adapted to the clinical situation. To this effect, the use of objective end results parameters is introduced, including MRI, MR Spectroscopy, PET Scanning, Tumor Markers and PSA levels. Typically, the treatment is continued with further reduced doses until all the objective parameters confirm a complete response or failure is determined. Therefore, as opposed to classic radiation therapy, patients are treated to effect as objectively demonstrated, instead of to a pre-determined radiation does or number of fractions. Patient Population Patients included in this study belong to a subpopulation that refuses all standard medical treatments, including clinical radiation therapy, surgery and chemotherapy. All signed appropriate consent forms. The recruitment period was from January 1999 to July 2012.

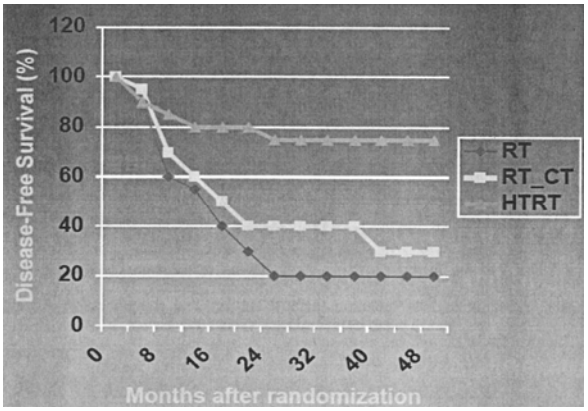
Statistics

All test were done with Graph Pad Prism 4 sohware (Graph Pad Sohware Inc., San Diego, (USA) using the method of Kaplan and Meier. Meta-analysis was done by directly extrapolating published survival date for each type of tumor and comparing to current results with HTRT.

Results

1. Toxicity was minimal considering the biological equivalent of radiation doses given. Dermatitis and occasional thermal buns 6% of treatments, muscositis, thickness of saliva and altered taste during head and neck treatment. Hyperthermia did not seem to add to the radiation early effects. In all, the treatment was well tolerated on the vast majority of the patients. Side effects were less than with curative radiation therapy alone. No Grade IV toxicity (Common Toxicity Criteria) was observed.

2. Complete response rates were gratifying. Results of thermoradiotherapy confirmed our previous experience. Breast tumors, showed a compete response rate (CR) of 82%. The CR rate for head and neck tumors was 88% and for prostate tumors 93%. Meta-analysis comparing HTRT with conventional radiation shows a 30 to 50% advantage for HTRT in terms of 5-year survival and response rate. Survival rates with HTRT were around 80% warranting treating early superficial tumors with HTRT alone.
3 Projected 5 year survival was at a very high level for early stage head and neck cancer upwards of 80% (Figure 1) In compliant patients which compares well with radiation therapy alone or chemradiation.
4 Comparison survival after treatment with HTRT versus chemo-radiation or EBRT (external beam radiation therapy). (Figure 1) depict the comparison in projected 5 years survival time between the 3 modalities (HTRT, EBRT and chemo-radiation)



RT = Radiation Therapy RT-CT= Chemo & Radiation
HTRT= Hyperfractionated Thermoradiotherapy
Figure 1. Percentage Survival Overtime Head and Neck Tumors – Callais, Q

Patients that completed the projected course of (HTRT) maintained the high percentage of 5 year survival (88%). (Table 1)

Response Rate of Compliant Head and Neck Cancer Patients

# of Patient	Response		Recurrence	Dissemination	Survival
	Complete # [%]	Partial # [%]	# [%]	# [%]	# [%]
45	40 [88]	5 [12]	5 [12]	5 [12]	40 [88]

Table 1. The mechanism of ICD. The process of the DAMP formation, immune-recognition and immune-activation

However patients that discontinued treatment before being medically discharged, the survival rate decreased to 20% (Table 2)

Compliant	Non-Compliant
88%	20%

Table 2. Survival Rate Compliant VS Non-Compliant

Discussion

A method is designed to treat superficial heatable tumors of the head and neck with curative intent when at early, non-disseminated stages-Higher response and survival rates can be achieved with less, more moderate toxicities than with EBRT or chemoradiation, as shown by Meta analysis, therefore we reached the following tentative conclusions, which apply only to compliant patients that successfully completed the treatment course.

The New and the Old New ONCOLOGY GOAL
OLD: DUMP and PRAY

- Give MAXIMUM DOSE of TOXIC TREATMENT MODALITY
- PRAY FOR RESULTS.

NEW:

- Use less toxic Thermoradiotherapy,
- TREAT to EFFECT, OBJECTIVELY DOCUMENTED

Conclusion

Protracted RT Hyperfraconoon with daily Hyperthermia.

- Decreases the side effects of radiation therapy.
- Allows treating to effect using objective end point parameters (tumor markers, PET scans, MRI, etc.).
- Accomplishes a high percentage of complete responses in superficial tumors.
- Accomplishes a high 5-year survival rate in the 80-90ti range in early superficial tumors.
- Is potentially curative in early stage breast, head and neck and prostate cancers.
- Is more effective and less toxic than radiation or chemotherapy.

The Future of Hyperthermia

1. Treat with curative intent
2. Find a niche where Hyperthermia will be included in the guidelines for the NOVO therapy. Suggestions: Head and Neck, Prostate, Breast, Sarcomas
3. Became part of institutional tumor boards to implement these objectives and accrue patients
4. Emphasize proven palliative effectiveness of Hyperthermia. Specially pain palliation (eg. Bone, pain, chest, wall recurrences, etc.) Design prospective, randomize multi-institutional trials to prove points 1, 2 and 4.

Summary

HTRT as previously described (20) consist of daily Hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180cGy to 100cGy resulting in protracted treatment time that decreases the isoeffect biological equivalent dose by 15% to 25%. This decrease is compensated by the increase number of hyperthermia fractions which potentiates each dose. Treatment is continued until an objective complete response is adained, or failure determined. 45 head and neck patients were treated with a follow-up of two to five years. All patients were early stage (less than III). However a cohort of 12 patients were non-compliant and discontinued treatment aher receiving at least 2/3 of the prescribed radiation dose.

Results

Compete responses were obtained in 88% in the compliant patient group- with 5 local recurrences and 5 cases of dissemination-the survival rate remains at 88%. In the non-compliant cohort complete responses were 20%, recurrences 11%, dissemination 80ti and survival 20%. Toxicity in both groups was equivalent. No grade IV side effects (common toxicity criteria) were observed.

Conclusion

Protracted hyperfractionation of daily thermoradiotherapy decreases the side effects of radiation therapy, allows treating to effect using objective and point parameters, accomplishes a high percentage of complete responses and a high 5-year survival rate in the 80-90% range in early head and neck tumors, where it can be considered as potentially curative. However compliance with the protracted regime is crucial to accomplish the desired results.

Deep Hyperthermia In Oncology

Prof. Dr. Andras Szasz, PhD[1]
(1) Biotechnics Department, St. Istvan University, Hungary

Introduction

Hyperthermia was one of the very first medical approaches. It was based on various religions and had deep philosophical roots in most of the ancient cultures. It was one of the popular "kitchen medicines" having various heating methods vivid in cultural wisdom of various societies. Probably this simplicity and natural character was one of the factors why the long history was not enough for its serious medical consideration despite the actually widely applied household techniques. Oncological hyperthermia (overheating the body partly or completely) was definitely the very first oncotherapy in human medicine. The general professional skepticism blocked its application for a long time.

Clinical realization

The main problematic point is the late start of clinical use of local hyperthermia for patients. The reason is the present protocols in oncology requesting to apply the "gold standards" (surgery, chemotherapy, radiotherapy) and their combinations until these are effective. In this point the patients start local hyperthermia late, when the curative phase is over, normally only palliation is possible. However, there is a local hyperthermia method, modulated electro-hyperthermia, (nanothermia or its popular name oncothermia), which is able to act curatively even in these late phases of the disease. Moreover, it could act systemically, reestablishing the homeostatic equilibrium of the body. Its synergy with immune-associated therapies like the traditional Chinese medicine (TCM) is proven in the labs and in clinical practice too.

Results

In laboratory use we had directly proven the great synergy of TCM herb treatment with oncothermia. The clinical results are also well supporting these preclinical indications. Presently oncothermia has 62 clinical trials altogether including more than 3700 patients from five countries (Germany, Hungary, Italy, S. Korea, China). These trials over 19 lesions: Bone (metastatic); Breast; Colorectal; Gliomas; Head & neck; Brain (metastatic); Kidney; Liver (metastatic); Lung (NSCLC); Lung (SCLC); Pancreas; Cervix; Ovary; Prostate; Soft-tissue sarcoma; Stomach; Urinary-bladder; Uterus. Average number of patients in the studies is 53, by lesions 116. Maximal patient number is a study (Phase III) was 311 (NSCLC). The average oncothermia enhancement ratio (ratio of the median survival of responders to non-responders) was 5.1. The comparison with the large databases was made in multiple clinics relations, showing extremely large (minimum 20%) enhancement of the 1st year survival percentages. Most of the treatments use immune-supporting therapies and the success is probably promoted by this supportive care too.

Objective

Our objective is to analyze the problems and present a solution by the electromagnetic mechanisms for effective hyperthermia in oncology, and show the clinical results by nanothermia (modulated electrothermia). This emerging method (popularly named oncothermia) is a presently applied in 28 countries in all the five continents of the world.

Conclusion

Oncothermia is a feasible treatment for oncology. Its results show the possibility to make curative treatment in high line applications when usually only palliation is applied. Its synergy with TCM is one of the most exciting tasks of future research.

Keywords

Deep hyperthermia, oncology

Narrowing the Gap: the position of hyperthermia between academic and complementary oncology

Ralph W. Moss, PhD[1]
(1) Cancer Decisions®, Lemont PA, USA

Hyperthermia developed simultaneously in the late 1970s in academic centers and various CAM cancer clinics. Each developed along parallel tracks that addressed the needs of the various constituencies. Specific companies then arose to address the needs of each community. Today, interaction between the two "camps" is sporadic at best and sometimes even hostile. Before broader cooperation can occur each side needs to understand the particular conditions that give rise to their differing approaches.

The goal of Academia is to raise hyperthermia to the status of a precise science, with the same degree of predictability as radiation oncology. This is ultimately a question of quality control. The precise dose of heat delivered to the tumor (but not to surrounding tissues) must be measured, either with probes or thermometric MRIs. A precise calculation must be provided to oncologists of the statistical improvement in tumor responses, disease-free (DFS) and overall survival (OS). Such knowledge is only obtainable through large multi-center, randomized phase 3 clinical trials, preferably published in high-impact English-language journals. Cost and toxicity are of minor consideration compared to the attainment of reliable information on the exact effect of treatment. To date, only 2 such phase 3 trials have been published, addressing only a tiny fraction of all cancer cases.

By contrast, CAM cancer clinics/hospitals emphasize treating patients according to their individual needs and desires. High heat is shunned because of complaints over side effects. Probes are out of the question. Patients are treated individually, not according to strict protocols. Costs are kept to a minimum, corresponding to the patients' ability to pay out-of-pocket. Formal phase 3 trials are impossible in this context because (1) one cannot isolate the treatment effect of hyperthermia from that of other elements in a holistic patient-centered program; (2) no manufacturer or single clinic can afford the cost of conducting a phase 3 trial; and (3) most clinical directors do not have sufficient knowledge, connections or expertise to conduct such trials.

The author will suggest strategies that could be employed to increase scientific knowledge coming from CAM clinics and thereby narrowing the gap between academic and CAM approaches to hyperthermia. This would increase acceptance of the field of hyperthermia as a whole.

Oncothermia Journal 10:35-39 (2014)

Ozone Therapy and Combined PRP Applications

Ruhi Cakir
(1) MediOzon Klinikleri, Istanbul, Turkey

Ozone Therapy and Combined PRP Applications

Aim

This presentation intends to expose the state of the art related to the clinical use of the combination of ozone and autologous plasma rich platelet (PRP) in different procedures which belong to the field of vascular medicine, traumatology and aesthetic medicine.

PRP: Historical Perspective

The enhancement of tissue healing by the placement of supraphysiologic concentration of autologous platelets. The application of PRP has been documented in many fields. First promoted by M. Ferrari 1987 as autologous transfusion component after an open heart operation to avoid homologous blood product transfusion. It was Dr Rita Levi Moltancini, who in 1948 discovers the Nervous Growth Factor that led her, along with Dr. Stanley Cohen, to obtain the Nobel Prize of Medicine in 1986, as well as the description of the epidermal growth factor by Stanley Cohen in 1962. The initial popularity of PRP grew from its promise as safe and natural alternative to surgery. Studies suggest that platelets contain an abundance of growth factors and cytokines that can affect inflammation, post operative blood loss, infection, osteogenesis, etc.

Platelets Rich Plasma

- Activated platelets release numerous proteins, among them adhesive glycoproteins and growth factors
- It shows that this therapy has been able to promote soft tissue regeneration with a decrease in infection rates, pain and inflammation. Clinical experiences show a clear improvement in wound healing after having used ozonized rich platelet plasma along with ozone therapy.

Research

Researches now show that platelets also release many bioactive proteins responsible for attracting macrophages, mesenchyme stem cells and osteoblasts that not only promote removal of degenerated and necrotic tissue, but also enhance tissue regeneration and healing.

Introduction

Activated platelets release:

- adhesive glycoproteins
- growth factors

Following subcutaneous injection, these proteins and GF interact with cells residing in the subcutaneous tissues, eg:

- skin fibroblasts
- endothelial cells
- osteoblasts

Upon binding to their cellular receptors, glycoproteins and growth factors activate intracellular signaling events, mediating:

- angiogenesis
- cell proliferation
- migration

- survival
- production of extracellular matrix proteins

What is Autologous Platelet rich plasma (A-PRP)

A-PRP is a concentration of human platelets in a small volume of plasma measured as 1,000,000 platelets per nm3 or 2-6 times the native concentration of whole blood at pH of 6.5-6.7.
Also referred to as

- autologous platelet gel
- plasma-rich growth factors (PRGFs) or
- autologous platelet concentrate
- PRP is also a concentration of seven fundamental protein growth factors that have been proved to be actively secreted by platelets to initiate all wound healing
- PRP includes 3 proteins in blood known to act as cell adhesion molecules: fibrin, fibronectin and vitronection
- soft tissue repair-face skin rejuvenation
- bone tissue repair – bone graft healing

By

- Collagen formation
- Extracellular matrix synthesis
- Fibroblasts proliferation
- Angiogenesis

The objective of the combination therapy

- To boost, to enhance the effect
- To demonstrate that the combination of both techniques, accelerates the lysate of the thrombocytes, especially if it has been anticoagulated with heparina (Bocci, 2003).

How does PRGF work?

1. PLT clotting – after 10 min – need anti coagulant.
2. De-granulation – release of content of PLT α-granules, that contain GF, by budding from PLT membrane and addition of side chains – Need Viable PLT!
3. GF bind to Receptors of the cells attracted to the wound.
4. Initiation of production of collagen and cell proliferation – Chemo attractant activity – attract Mesenchymal stem cells to the wound.
5. Formation Of EXTRA CELLULAR MATRIX.
   = Acceleration of normal wound healing process.

How are platelets activated?

Dermal collagen and exposed endothelial collagen

- Arachidonic acid (inflammation pathway)
- Thromboxane A2 (Inflamation)
- ADP
- Thrombin
- Vasoporessin
- Adrenalin
- CaCL2
- Controlled heat (radio-frequency)
- Vibration
- Medial Ozone

PRP activation

PRP must be activated prior to injection and it can be activated exogenously by:

- Thrombin
- CaC12
- Mechanical trauma
- Medical Ozone

Once PRP is activated, a fibrin network begins to form and creating a fibrin dot or membrane. If PRP is activated too strongly, the fibrin network will be bivalent, unstable network. If it is activated in a more physiologic manner, a tetramolecular stable network forms that enhances enmeshment of cells and GFs. Although this can be useful for surgical procedures, it is undesirable to have the PRP overly viscous when injecting into soft tissue!
Activation results in rapid GF release, with 90% prefabricated factors releaseminutes.d in ten. Many GFs have short half-lives so greatest effectiveness may result if they are activated at or just prior to injection. Most commercial PRP kits do not activate PRP. Some replace Calcium that was bound by ACD to create a more physiological state. Employing inactivated PRP is used in soft tissue, it does not need to be exogenously activated. To avoid unintentional activation of platelets most protocols use large needles (>22) to draw the blood and re-inject PRP.
Collagen is a natural activator of PRP thus when PRP is used in soft tissue, it does not need to be exogenously activated. Once activation has occurred at the injection site, release of growth factors initiates an inflammatory response that last approximately 3 days.
Fibroblast s accumulate at the site of injection, which marks the beginning of the proliferate phase of healing that last several weeks. Remodeling occurs to the collagen matrix that was laid down by the fibroblasts. This remodeling phase that leads to the formation of mature tissue lasts about 6 months. It takes 3 phases for new tissue to form and provide long-term stability to tissue.

Growth Factors

Mitogenic Agents: The control and stimulate the cellular proliferation
Motogenic Agents: They control and stimulate the cellular migration
Angiogenic Agents: They promote the creation of new blood vessels
Cito-protectors: They stimulate the cellular survival aggressions can turn out to be lethal to the cells.
Agents that induce the formation of matrix bone and the collagen synthesis.
Agents with antibacterial effects against Staphylococcus aureus and Echerichia coli.
Agents that even have anti-inflammatory properties come up as the blockade of the protein MCP-1 and generation of lipoxina A4.

PDGF aa PDGF bb PDGF ab	Platelet derived GFs	Activated thrombocytes
TGF-alpha TGF-beta	Transforming GFs	Activated Thrombocytes
IGF-I IGF-II	Insulin-like GFs	Activated thrombocytes
EGF	Epidermal GFS	Activated thrombocytes
VEGF	Vascular endothelial GFs	Leucocytes and endothelial cells

PDGF (Platelet Derived GFs)	**- Chemo-attractive to Mesenchymal Scsand endothelial cells** **- Differentiation for fibroblasts** **- Promote the synthesis of extracellular matrix**
TGF (Transforming GFs)	- Promotes cell mitosis - Significally increases the synthesis of collagen - Stimulate DNA synthesis - Proliferate various types of cells
VEGF (Vascular Endothelial GFs)	Stimulate angiogenesis
EGF (Epidermal GFs)	Regulate cell growth, proliferation and differentiation
IGF 1 and 2 (Insulin-like GFs)	Stimulation, proliferation and differentiation or different cell types

Growth Factor	Source	Function
Transforming Growth Factor-beta, TGF-ß	Platelets, extracellular matrix of bone, cartilage matrix, activated TH_1 cells natural killer cells, macrophages/ monocytes and neutrophils	Stimulates undifferentiated mesenchymal cell proliferation; regulates endothelial, fibroblastic and osteoblastic mitogenesis; regulates collagen synthesis and collagenase secretion; regulates mitogenic effects of other growth factors; stimulates endothelial chemotaxis and angiogenesis; inhibits macrophage and lymphocyte prolifeation
Basic Fibroblast Growth Factor, bFGF	Platelets, macrophages, mesenchymal cells, chondrocytes, osteoblasts	Promotes growth and differentiation of chondrocytes and osteoblasts; mitogenetic for mesenchymal cells; chondrocytes and osteoblasts
Platelet Derived Growth Factor, PDGFa-b	Platelets, osteoblasts, endothelial cells, macrophages, monocytes, smooth muscle cells	Mitogenetic for mesenchymal cells and osteoblasts; stimulates chemotaxis and mitogenesis in fibroblast/glial/smooth muscle cells; regulates collagenase secretion and collagen synthesis; stimulates macrophage and neutrophil chemotaxis
Epidermal Growth Factor, EGF	Platelets, macrophages, monocytes	Stimulates endothelial chemotaxis/angiogenesis; regulates collagenase secretion; stimulates epithelial/mesenchymal mitogenesis
Vascular endothelial growth factor, VEGF	Platelets, endothelial cells	Increases angiogenesis and vessel permeability, stimulates mitogenesis for endothelial cells
Connective tissue growth factor, CTGF	Platelets through endocytosis from extracellular environment in bone marrow	Promotes angiogenesis, cartiage regeneration, fibrosis and platelet adhesion

What is Ozone?

Three atomic Oxygen – Trioxygen
Molecular formula is O3
Has very light blue colour in gas form
Second the strongest Oxidant – Electron donor
Can kill all known bacterias, viruses and molds by rate 99.9%
Harmful to all living organisms over some limits
Dose concentration and effect time are parameters on damage

Medical Ozone

Therapeutic Medical Ozone is a combination of pure oxygen and ozone in microgram doses 0,05% O3 – 5% O3.

Figure 1: Growth factors acting on 'healing cascade'

Factor	Name	Principal source	Effects
PDGF aa PDGF bb PDGF ab	Platelet derived growth factors	Activated thrombocytes Activated thrombocytes	Mitogenes of mesenchymal stern cells promote the synthesis oft he extracellular matrix
TGF-alpha TGF-beta	Transforming growth factors	Activated thrombocytes	Stimulation of DNA synthesis proliferation of various types of cells. Favours the synthesis of collagen
IGF-I IGF-II	Insulin-like growth factors	Activated thrombocytes	Stimulates proliteration and differentiation of osteoblasts
EGF	Epidermal growth factor	Activated thrombocytes	Stimulates proliferation and differentiation of epidermis cells, co-stimulating angiogenesis
VEGF	Vascular endothelial growth factor	Leucosytes and endothelial cells	Stimulates angiogenesis and chemo-attraction of osteoblasts
In addition, the activated thrombocytes have on their surface a multitude of signalization molecules, for example: CD9. CD-W17. CD31. CD41. CD42a-d. CD51. CD-W60. CD61. CD62P. CD63			

99,95% O2 – 95% O2
1 μg /ml – 100 μ/ml O3

The Ozonized PRP apparently contributes to

Advantages of the combined therapy Ozone+PRP
Effective in a high 95-98% of cases
It is possible to apply to all range of aging groups.
It avoids the surgery in high amount of cases
It does not invalidate the surgery if it is necessary.
It is ambulatory, it avoids internments, anesthesia, post-operative, special care and recovery times.

Advantages

It is a conservative, minimally invasive treatment that respects the anatomy and physiopathology of the organism. It is correct to the cause, the imbalance of the organism and does not silence the symptom of alarm that in this case is the pain. Avoid the use of medicines along with its side effects.

Ozonized PRP in wound healing

In wound healing platelets, it plays an essential role since they are rich in platelet derived growth factor (PDGF); transforming growth factor-b (TGF-b); vascular endothelial growth factor (VEGF). Mustoe et to. demonstrated in experimental model, that only one PRP dose was increasing the volume of granulation of the tissues in 200 % after 7 days. Some of the proteins liberated by the thrombocytes are absent in chronic wounds which contribute to the abnormal repairing tissue process. This is an evidence of the important role of these substances in the repair tissue process.

Oncothermia Journal 10:41-43 (2014)

The Cultural Traits and Scientific Significance of the TCM Psychology

Hongzhong Qiu[1]
(1) University of Guangzhou Chinese Medicine

The Cultural Traits and Scientific Significance of the TCM Psychology

With the increasingly advanced western psychology today, why should we still endeavor to study Chinese traditional medicinal psychology? That is because clinical psychology is a serving undertaking, whose effect depends on how much the psychological theories and methods stay in line with the consultative object's cultural background. Yet currently the clinical mental consultation in our country is basically copying and imitating the western psychological theories and methods. In fact, the western psychology was deeply rooted in the western history and culture, penetrated with westerners' philosophy, believes, value and life experience. Western psychology takes physics as its mode, purporting demonstration and attempting to construct it as a precise and objective natural science. Although scholars have accumulated a great amount of demonstrative data, they consider all the consciousness experiences, philosophical psychology as well as all the traditional, indigenous, experienced and daily psychology as pre- or non-science, which disables western psychology from exploring the rich human inner worlds and the really existing experience in daily life, which has greatly narrowed down the vast realm of the studies on human mental states, and which lacks the nourishing of the abundant, great and historical mental culture.

Under this background, it plays an extremely important role in both scientific research and practicality to coordinate and excavate the ideology and technology of traditional medicinal psychology. Chinese traditional medicinal psychology boasts not only age-old history and unique theory, but also abundant clinical skills and proved recipes, and can completely match in excellence with western clinical psychology.

1. The cultural characteristics of Chinese traditional medicinal psychology

Compared with western clinical psychology, the Chinese traditional medicinal psychology has own special cultural characteristics, from the angle of post-modernism; this kind of difference probably means the existence of another possible science pattern.

1.1. Chinese medicine particularly emphasizes the interaction between physique and spirit – the theory of the five internal organs originates form Taoist, which has its explanation of physiologic psychology and nerve psychology. According to the Chinese medicine, people's mental activities base upon their physiology. But different from western psychology, Chinese medicine does not believe a person's emotion is related only to the structure and function of the brain, but insists on "the theory of external cause of diseases" of one's emotion, which says "Man has five viscera, which may bring on five moods (visceral-qi) to produce joy, angry, grief, melancholy and fear". Anger impairs the liver, joy impairs the heart, anxiety impairs the spleen, melancholy impairs the lung, and fear impairs the kidney."
"The theory of external cause of diseases" of the Chinese medicine constituted a kind of compatible disjunctive logic with "the central pivot theory" of western psychology. The point of five internal organs holding spirits in Chinese medicine urges us to reconsider the relation between oru body and emotion and disease mechanism: Would the condition of internal organs influence our mood? Or would radical emotion affect the internal organs? Can we adjust our mood by means of taking medicine so as to regulate neurotransmitter level and hormone metabolism?

1.2. Chinese medicine emphasizes the uttermost importance of mental adjustment in health care and medical treatment, which derived from the ego consciousness of Taoist theory, in line with

psychoanalysis and personality rebuilding treatment. From the point of Chinese medicine, a person's ego consciousness has very important influence on the conditions and processes of his internal organs. The heart controls mental and emotional activities, and is regarded as the dominant one among the internal organs, and the motion of heart may cause the moving of other organs. "Stay quiet may hold the spirit, while rashness can lead to perishing." If one "remain nonchalant and void, then genuine qi will flow; keep a sound mind, how can diseases come on?" On the contrary, if one has "decline spirits and mental confusion, his disease cannot be healed."
Both the Taoist Zen and Chinese medicine think people can acquire a good and balanced health condition by means of active ego activity (such as keeping a sound mind). This is different in approach but equally good with the effect of modem creatural feedback technology. The most typical methods of remain nonchalant and void is to practice the inner elixir exercise. Before the psychoanalysis school divided consciousness into two parts and started carrying out analysis on psychology, Zen Taoist had already separated the structure of "mind" in two, namely spirit and soul.
The so-called "spirit" is the life, character and vigor inherited from parents and surmounting space-time. And "soul" refers to the acquired characters, relying on the external world, fluid, subjected to environmental influence easily and leading to happiness, anger, grief, joy, lust for flesh and wealth, as well as contending for power and forfeit.

The Inner elixir exercise can be defined as a psychological therapeutic method that originates from Confucianism, Taoism and Zen, by means of cognition, attitude, mood and behavior change, taking satori as the chance, with a target of personality reconstruction.
The cross-cultural comparative research reveals that inner elixir exercise contains myriad elements of mental therapy such as western psychoanalysis, reasoning-emotion treatment, behavior psychological treatment, Gestalt psychology treatment, satori, existentialism, etc. C.G. Jung eventually found that the inner elixir exercise identifies with his mental treatment.

1.3 Chinese "Yin Yang five states" corporeity-personality theory believes the integration of body and mind, and coincides with modern gene biology and clinical dialectical therapy. The principal feature of Chinese traditional personality theory is its comprehensiveness, showing its obvious clinical functions, which means that various characters correspond with certain figures, and with certain physiologic, pathologic characteristics and certain treatment principles.

2. The realistic meaning of inheriting and developing Chinese medicine psychology

2.1 It helps us to hold and develop thoroughly the humanism in traditional Chinese medicine. Chinese medicine is based on humanism: it is aware that human being is natural create and he must hold to the natural rules, while on the other hand, it admits human mental activities and his social attribute, and even regard his ego consciousness as the ultimate feature which distinguishes him from other animals. "A patient with vitality is apt to recover from the illness, while there is a poor prognosis for a patient without vitality." The humanism of traditional Chinese medicine is also adequately demonstrated by the basic treating rule of meeting patients' mental needs. If we only take creature substantial evidence as the same as the modernization of traditional Chinese medicine, and if we believe scientific research contains the all of Chinese medicine research, we may deviate from the scientific humanism of Chinese medicine.

2.2 It helps us to understand the characteristics of epistemology and the methodology in Chinese medicine. Chinese medicines always described and defined the objects from the relation of the principal part and its object. And its theories always concerning about the understanding relation in "I- you" to comprehend the body organ, physiology phenomenon and disease phenomenon. For

example, “the visceral manifestation theory” reflects how TCM gathers it knowledge and the basic characteristics of things.
In the past, many modern Chinese medicine researchers failed to explain the theory of “visceral manifestation” with demonstration because they didn’t know the psychology meaning in the Chinese medicine theories.
The way we observed and experienced the object in sense of recognition and psychology does not equal to matter itself, because this object had been concluded into the structure of the activity realistically brought by the subject, and referred to those objects subjectively. This is to say, many principal concepts in Chinese medicine have something to do with the thinking enactment of corpus, consciousness of direction and particular mental activity (such as four physical examinations).

2.3 It helps to prevent the medical science realm false science. It was a terrible lapsus to mistaking the mental experience as physiological one, and study the concepts as concrete substance, Researchers paid no attention to the research of the medical culture and Chinese medicine psychology, ignored the connection between science and humanities, which was led by cognition mistake. The "False Qi Gong" phenomenon was an inspiring social activity in our 20 century. "Inner elixir exercise" has a very history in China, which interjects Taoist theory of Zen, advocate people to cultivate one's heart. In 20th century, the exercises once again become a very popular body exercise for mass population to enhance their health after several decades' evolvement. But to our disappointment, just because the misunderstanding of the culture and explanation of "inner elixir exercise" resulted in so many modem "mental tragedies". It was proved again and again, only to explain the original meaning and the psychology essence of "inner elixir exercise" in a right reasonable way, then can prevent from "false science" to its exploitation. C.G. Jung is the first westerner who explains the original, mental mechanism and medical treatment of "inner elixir exercise" with the modern psychology. His epistemology and methodology inspired us to see clearly of the essence of "inner elixir exercise" and to expose the "false Qi Gong".

Conclusion

Chinese people, Chinese heart, we need to analyze and settle our own knots in Chinese way. The American cross-cultural psychologist TRiandis C·H says "Before I got everything I need from China, it is impossible for psychology to become a widespread and valid science. Because China has a very large proportion on population; and as to the cross-cultural psychology, China has to examine all the results of psychology from a new background. While they are doing like this, the Chinese psychologists should tell the western psychologists, which concepts, measurement, cultural and historic factors can revise the psychology result of past.
Prospecting future, the development of psychology in the natural science and humanities, science psychology and native psychology will be a new and inevitable trend. From the past unitized science psychology, the psychology of contemporary has already headed for a multi-, complex, prosperous psychological cultural development. Therefore, the studies and researches of Chinese clinical psychology will certainly do a lot of contribution.

Oncothermia Journal 10:44-44 (2014)

Toward a Radical Cure – with a Focus on Diagnosis of Patient's Defense Level and Treatment of Replacing Electrons

Horiguchi Hiroshi[1]
(1) Director of Horiguchi Hospital, Japan

Today, we are not satisfied by achieving medical improvement, but curing the disease. However, traditional western medicine can not solve all of the medical problem, so it is important that we should find the solution to eliminate the "causes of disease". "Self-defense capability diagnosis" is one of the method to find the causes of disease. In this paper, I am going to illustrate the mechanism and the theory of replacing electrons therapy, which will be popular in the medical field in the near future.

Does high dose injectable Vitamin C work as an oxidant or as an antioxidant or both in cancer treatment?

Ian Dettman[1]

(1) Australasian College of Nutritional and Environmental medicine

In vitro Vitamin C (Vit C) is known to kill cancer cells in a dose/concentration dependent way. In animals and patients high dose Vit C also is effective in cancer and higher dose/concentration is more effective. Protocols are used that get very high plasma concentration. There are many theories about why this works. One very popular theory is the pro-oxidant theory. Extracellular matrix (ECM) contains proteins which contain redox active metals like Cu or Fe. Vitamin C in the ECM reduces these protein bound metals ($3^+ \rightarrow 2^+$). The metals then react with molecular oxygen to form superoxide (0_2). 2 superoxide molecules react to form hydrogen peroxide (H_2O_2). This is called dismutation and might require enzymes (SOD). Two superoxide molecules react to form hydrogen peroxide (H_2O_2). This is called dismutation and might require enzymes (SOD). The pro-oxidant theory says that the presence of Vit C (a reducing molecule) forms H_2O_2. H_2O_2 is an oxidizing molecule. H_2O_2 causes cancer cell damage/death. This has been demonstrated many times. The pro-oxidant theory shows that the amount of H_2O_2 produced increases with the amount of Vit C present. This all happens in the ECM. The H_2O_2 produced diffuses over the cancer cell membrane and affects the cancer cell directly. It may tum on cell death mechanisms. This pro-oxidant effect may work with any high dose reducing agent. In cancer treatment Vit C is used because it is safe in very high doses and can get very high concentrations in the ECM in a patient. The Vit C must be in its reduced form, i.e. ascorbate. Otherwise it does not work. The vitamin C as ascorbate is a reducing agent. This means it is an electron donor (it gives an electron). This is all it does.

This is how antioxidants work. For Vit C to give an electron to form H_2O_2 these must be in the ECM: Molecular O_2 and A redox active protein with Cu or Fe metal ions that can react with Vit C and O_2. ECM will contain various proteins which contain redox active metals. But ECM may not contain a lot of molecular O_2. O_2 is usually bound in transporters.In vitro there is always O_2 present in the medium because the medium is exposed to air. The medium may also be exposed to light and some redox active proteins are activated by light. Another problem with using medium in in vitro experiments is that the medium is different to ECM. The results might not be the same as in living systems. Another problem with using medium in in vitro experiments is that the medium is different to ECM. The results might not be the same as in living systems. Another problem with using medium in in vitro experiments is that the medium is different to ECM. The results might not be the same as in living systems. Experiments in medium can produce in vitro artefacts. When experiments to test the pro-oxidant theory have been tried in animals the ECM has been extracted to test for H_2O_2. This means that the samples are exposed outside the body, the results might not be the same as what happens in the living animal. So is Vit C a pro-oxidant or an antioxidant in cancer treatment? It has been shown that in exposed solutions Vit C can produce H_2O_2
We already know this happens in in vitro cancer experiments. It also happens in TPN solutions. This does not mean that this happens in the ECM of animals or patients. This has not been proved at all. Vit C is a very reactive molecule. It produces all kinds of results in in vitro experiments that do not happen in living animals.

All that Vit C does is give an electron. In this way it is always an antioxidant. Does Vit C have a pro-oxidant effect? It has not been proved that the pro-oxidant theory is true because it has not been proved yet in living animals. High dose Vit C in patients almost never has the same spectacular effects on cancer cells seen in test tube experiments. But Vit C is effective in cancer patients. Is the Vit C doing something else in living patients?

There are many other ideas about why Vit C works in cancer patients. The pro-oxidant theory has not been proved but at present it is the most popular theory about why Vit C works in cancer.

Oncothermia Journal 10:46-46 (2014)

The Current Situation and Development of Hyperthermia Technology in Integrated Cancer Treatment

Liu Jia[1], Zeng Yuanli[1]
(1) Oncology Radiation Department, Hunan Cancer Hospital, China

1. The current situation of thermal therapy and the basic assessment

1.1. Description of tumor thermotherapy

The current tumor thermotherapy technology, from the beginning simple technology, has gradually formed a kind of new and high technology based on the electronic, computer, optical, electromechanical, aerospace and aviation technologies. Using devices such as microwave, radio frequency (rf), laser, ultrasound, magnetic mediated, it can carry out six big classifications for the treatment of tumor, namely deep/intracavity thermotherapy, hyperthermia, whole-body hyperthermia, high intensity focused ultrasound (HIFU), minimally invasive thermal ablation, and magnetic induction hyperthermia.
Compared with other treatments, the thermotherapy, with nonionizing radiation, the toxic and side effect is far lower than the surgery, radiotherapy and chemotherapy; and its curative effect is also no less than the targeted drug treatment and immunotherapy and it has more advantages in price.

Oncothermia Journal 10:48-56 (2014)

Cancer, Inflammation and The Role of Nutrition

Tuomas Westermarck[1], Marika Crohns[1], and Faik Atroshi[1]
(1) Pharmacology & Toxicology, 00014 –University of Helsinki, Sanofi-aventis Oy, Helsinki, Finland

Cancer, Inflammation and The Role of Nutrition

Abstract

Cancer is a disease with multiple interwoven causes and the role of diet has become a well-recognized factor in cancer incidence. It has also been described as “wounds that fail to heal”. Cancer is due to accumulation of DNA mutations that confer a growth advantage and invasive properties on clones of cells. A variety of factors have been studied in relation to cancer including, nutritional deficiencies, chemical carcinogens, physiological conditions, habits, infections, medications and socioeconomic interacting with genetic susceptibility influence the accumulation of mutations in cells. There are many different types of cancers.

Some cancers will have tumours and others are cancers of the blood that do not have visible growths. Not all tumours are malignant; some are benign and are simply a tumour that can be surgically removed and the patient will recover. Other types of cancer are more insidious and cannot easily be treated. Fortunately, there are now treatment options for most cancers and those treatments are improving all the time. Chronic inflammation is associated with a high cancer risk. There is increasing evidence for close correlation between inflammation, the microenvironment and tumour-associated neo-angiogenesis causing the adverse outcomes of cancer. Good nutrition is the bridge to better health and may help lowering the risk of many diseases. Nutrition is important at every stage of carcinogenesis from initiation to promotion to progression and metastasis and.

Proper nutrition in the diet along with certain behavioural changes including lifestyle and environmental factors may help to maintains health. Although it is difficult to prove that eating certain foods can cure cancer, however, eating a wide variety of foods helps to ensure you get all the nutrients you need. While certain risks are un-changeable (genes for example), some lifestyle factors if modified may help reduce cancer risk. However, the relationship between the two is often very complicated and we don't yet have all the answers, but the message appears to be very simple - eating healthy and exercising for a strong body also applies to fighting cancer. It is premature to say that we can keep cancer from forming or returning through diet and exercise, however, it at least seems clear that we can better our odds against it. Not all health problems are avoidable, but one have more control over his/her health than one may think. Whether a person with a history of cancer in his family or are currently battling the disease a change in lifestyle factors can make a difference in helping to fight off cancer. It is also important to point out that some foods (food contaminants) actually increase the risk of cancer, while others support the body and strengthen the immune system. The challenge, however, is finding a consensus about which dietary changes you should make, or which types of diets can trigger certain cancers. For example, it's suspected that breast cancer might be caused by a high-fat diet, being overweight or obese which leads to the release of certain hormones in the body. However, no clear evidence exists to make that a proven fact right now.

Some risk factors are well established, such as smoking's link with lung cancer. But others are less recognised. And for oesophageal or gullet cancer, half of the risk comes from eating too little fruit and veg, while only a fifth of the risk is from alcohol. For stomach cancer, a fifth of the risk comes from having too much salt in the diet, some cancers, like mouth and throat cancer, are caused almost entirely by lifestyle choices, the studies shows. By making a good food choice, one may protect his/her health.

Introduction

Cancer is considered to be a complex multistep disorder, the result of a combination of factors including exposure to radiation and/or carcinogens (damage to DNA), infection, genetics, aging, immune function disorders, and lifestyle factors such as smoking (Nelson et al. 2003; Mahan & Escott-Stump, 2004; Kamangar et al.2009). A variety of external factors including nutrients in the environment interacting with genetic susceptibility influence the accumulation of mutations in cells. Nutrition is important at every stage of carcinogenesis from initiation to promotion to progression and metastasis. Therefore, Cancer may be regarded as a complex metabolic deficiency disease. Clinical trials have evaluated the effect of dietary nutrients on tumour development (Tallberg and Atroshi, 2011; Tallberg et al.2011). These dietary agents may help to suppress the transformative, hyper proliferative and inflammatory processes that initiate carcinogenesis. In traditional Chinese medicine feeding patients with exotic herbs could cure them. At that time it was impossible to analyse the precise functional factors ingested, but we seem now to have reached an academic form of traditional Chinese medicine since we can include specific pure alimentary components to construct a supportive curative diet. Spontaneous regression of cancer is rare, and has been called "The metabolic triumph of the host". It implies that these patients by chance have ingested a complicated combination of bio-modulating natural components to regain observations signify that the complex metabolic deficiency triggering cancer, and also genetic weaknesses, can be compensated by feeding patients specific functional alimentary components. Therefore, a biological, economical and non-invasive treatment modality is needed.

Cancer develops when cells multiply in the presence of oxidation and other damage. According to micro-evolutionary models, cells become damaged and change their behaviour, growing uncontrollably, and act like the single-celled organisms from which they originally evolved. The cancer cells' individualism overwhelms the cooperative control processes that are essential to a complex multicellular organism. Importantly, antioxidants limit oxidative damage and thus inhibit early benign cancer growth, preventing cancer from developing. Cancerous tumours results from a series of genetic changes having to do with cell division and growth control and genetic instability, mortality, the suicide mechanism in cells; the ability of the cells to migrate; the ability of the cells to attract to them a blood supply. Cancers represent a revolt within our bodies in which some cells have decided selfishly to go their own way, propagating their individual genes at the expense of the body as a whole. There are many forces that can prompt this internal uprising. Often it is mutation, damaged DNA, switching on genes. That is, cancer develops from changes that cause normal cells to acquire abnormal functions. These changes are often the result of inherited mutations or are induced by environmental factors such as UV light, X-rays, chemicals, tobacco products, and viruses. Several environmental factors affect one's probability of acquiring cancer. These factors are considered carcinogenic agents when there is a consistent correlation between exposure to an agent and the occurrence of a specific type of cancer. The effect of environmental factors is not independent of cancer genes. Sunlight alters tumour suppressor genes in skin cells; cigarette smoke causes changes in lung cells, making them more sensitive to carcinogenic compounds in smoke. These factors probably act directly or indirectly on the genes that are already known to be involved in cancer. Individual genetic differences also affect the susceptibility of an individual to the carcinogenic effects of environmental agents. About ten per cent of the population has an alteration in a gene, causing them to produce excessive amounts of an enzyme that breaks down hydrocarbons present in smoke and various air pollutants. Cancer appears to result from a combination of genetic changes and environmental factors. A change in lifestyle that minimizes exposure to environmental carcinogens is one effective means of preventing cancer. Individuals who restrict their exposure to tobacco products, sunlight, and pollution can greatly decrease their risk of developing cancer. Many foods contain antioxidants and other nutrients, such as colourful fruits and vegetables that may help to prevent cancer. These foods supply ample amounts of vitamin A, C, and E, as well as phytochemicals and other antioxidants that may help to prevent cancer. Eating the right kinds of foods during and after treatment can help you feel better

and stay stronger. Therefore, Cancer prevention is easier than you think. With a few simple lifestyle changes, you can drastically reduce your risk of many types of cancer. Many factors play a role in cancer development, but the good news is that most can be avoided.

The number of cancer cases around the world is increasing. The incidence has been associated with ageing, environmental factors and changes in lifestyle. Based on some research in animals and people, certain dietary measures have been suggested to prevent the progression of cancer. However, there is no solid evidence a healthy diet can prevent people developing cancer. The reasons that patients with cancer are using the dietary supplements are to enhance their health. However, consuming such dietary elements may also be at risk for drug interactions. By 2020, the world population is expected to have increased to 7.5 billion, of this number, approximately 15 million new cancer cases will be diagnosed, and 12 million cancer patients will die (Ferlay et al. 2010, Jemal et al. 2011). It is estimated that 7.6 million cancer deaths occurred worldwide in 2008. Lung (1.4 million, 18.2% of the total for men and women), stomach (0.7 million, 9.7% of the total for men and women), liver (0.7 million, 9.2% of the total for men and women), colorectal (0.61 million, 8.1% of the total men and women) and female breast cancers (0.5 million, 6.1% of the total for women) were the most common causes, accounting for more than half of all cancer deaths (Ferlay et al. 2010, Jemal et al. 2011, Soerjomataram et al. 2012).

Antioxidants are substances that prevent damage to cells caused by free radicals. Free radicals are molecules that have lost an electron, thus are unstable (Atroshi & Westermarck, 2005). These free radicals basically steal electrons from other molecules in effort to heal themselves, ultimately creating new free radicals in the process. By stealing electrons, it can cause damage to DNA, leading to the possible development of cancer.Antioxidants search for these free radicals and lend them an electron. This stabilizes the molecule, thus preventing damage to other cells. Antioxidants also turn free radicals into waste by products, and they eventually get eliminated from the body. They also have the ability to repair previous damage to cells. Free radicals are formed from a number of causes. Cigarette smoke, pollution, exposure to sunlight all causes the formation of free radicals. Other factors include normal daily processes like food digestion and breathing. Numerous animal studies have been published demonstrating decreased tumour size and/or increased longevity with a combination of chemotherapy and antioxidants. Our knowledge of antioxidants in a cancer setting is still at its infancy stage. The interactions between antioxidant and chemotherapeutics cannot be predicted solely on the basis of presumed mechanism of action when used concurrently. Fortunately, a large body of evidence is available to show a positive effect of high dose repeated use of antioxidants in the period before, during and after conventional cancer therapy.

Inflammation and Cancer

There is emerging evidence for a role of inflammation in the pathogenesis of cancer. Inflammation is known to cause DNA alterations. Chronic inflammation due to infection or injury is estimated to contribute to 25% of all cancers in the world. In recent years the relationship between cancer and oxidative stress has been extensively studied. Oxidative stress has been suggested to play a key role in carcinogenesis. Free radicals have been shown to mediate the anti-cancer actions of many chemotherapeutic regimens. Nonetheless the exact role of free radicals especially during cancer treatments is still largely unknown. Despite active investigation, knowledge is lacking concerning the local and systemic effects of free radical-generating treatments in cancer. Also radiotherapy exerts its cytotoxic effects through free radicals, either by direct action on DNA with damage as a consequence or indirectly by producing reactive oxygen species (ROS) (Figure 1). Many cancers are associated with increased production of ROS. The pathogenesis of cancer is a multistage process which involves mutations in critical genes required for maintenance of the cellular homeostasis. Oxidative mechanisms have a role in the initiation, promotion and progression of

carcinogenesis. This review will discuss free radicals involvement and the elevation of certain markers of oxidative stress in cancer with particular focus on the role of different antioxidants.

Most human disease is due to chronic inflammation resulting in loss of function of a joint, a blood vessel or an entire organ. In some organs, such as the heart and brain, acute inflammation can be fatal. Interleukin-1 (IL-l) is a master cytokine of local and systemic inflammation, and the availability of specific IL-l-targeting agents has revealed a pathological role of IL-l-mediated inflammation in a growing list of diseases (Dinarello et al. 2012). Oxidative stress is a major by-product of cellular metabolism and its regulation is critical for preventing disease and aging. Levels of reactive oxygen species (ROS) are generally higher in proliferating tumour cells than in normal cells and this may explain why ROS is a key component in the efficacy of chemotherapeutic drugs. There is evidence that carcinogens originated from food in some instance and the antioxidants can inhibit the activities of certain mutagens (Watson and Leonard, 1986).

Cancer as age - related diseases, Link between Faster 'Biological' Aging and Risk of Developing Age-Related Diseases

Although heart disease and cancers are more common as one gets older, however, not everyone gets them, and some people get them at an earlier age. It has been suspected that the occurrence of these diseases may in part be related to some people "biologically" ageing more quickly than others. Living cells have three main systems for protection and repair under oxidative stress (1) direct antioxidant enzymes (SOD, catalase, peroxidises), (2) proteases and phospholipases activated buy oxidative modification of membranes, (3) lipid and water soluble antioxidants. There is large number of physiological and pathological sources of oxygen radical and related compounds. A number of known exogenous agents are known to generate radical's species and thus increase the oxidative stress. Such agents include for example metal ions, pesticides, photochemical smog, ozone, ionizing radiation, tobacco smoke, numerous toxic chemicals and drugs. Importantly, it has also been well documented that a variety of endogenous processes are significant generators' reactions, mitochondrial electron transport, cytochrome P-450 detoxification reactions, phagocytic oxidative bursts, xanthine oxidase and lipid peroxidation etc. Lipid peroxidation has been suggested to be responsible for numerous deleterious effects observed in biological systems since it continuously proceeds by free radical reaction mechanisms after initiation. If this reaction is not terminated, a continuous self-feeding chain reaction is proceeding, making lipid peroxidation a good candidate to cause a variety of human pathology and possibly to participate in the prostate cancer processes.

Free radicals and formation of cancer

In recent years the relationship between cancer and oxidative stress has been extensively studied. The pathogenesis of cancer is a multistage process which involves mutations in critical genes required for maintenance of the cellular homeostasis (Powell et al., 2005). Oxidative mechanisms have a role in the initiation, promotion and progression of carcinogenesis (Toyokuni et al., 1995, Cooke et al., 2006; Ounjaijean et al. 2011). Oxidative DNA modifications are more common in cancerous tissues than in surrounding cancer-free tissues, which reinforces the conception that ROS play a role in the development of cancer (Jaruga et al., 1994). Persistent oxidative damage to DNA or impairment of antioxidant defence systems have been linked to mutation, activated transcription factors, modification of gene expression and chromosomal aberrations, i.e. genomic instability, processes which have been described in the progressions of cancer (Toyokuni et al., 1995, Morabito et al., 2004).

Inflammation is known to cause DNA alterations (Cooke et al., 2003). Chronic inflammation due to infection or injury is estimated to contribute to 25% of all cancers in the world (Coussens and Werb, 2002). Various chemical carcinogens such as chlorinated compounds, metal ions, barbiturates, phorbol esters, aromatic hydrocarbons and some peroxisome proliferators have been shown to induce oxidative stress and damage to DNA. They may therefore partly account for the development especially of work-related cancers. Very rare hereditary diseases such as Xeroderma pigmentosum, Franconia's anaemia and Cockney's syndrome are also associated with an increased cancer risk due to deficiencies in nucleotide excision repair (NER) (Powell et al., 2005).

Many cancers are associated with increased production of ROS (Toyokuni et al., 1995, Cooke et al., 2006).
The increased oxidative stress in cancer may be attributable to a variety of factors:
(1) Increased formation of ROS when the antioxidative defence mechanism works normally
(2) Unchanged status of exposure to ROS while the antioxidant defence mechanisms are decreased
(3) Failure in repair of oxidative damage, which leads to increased presence of ROS
(4) Combination of the above (Halliwell, 2007).

Free radicals and oxidative stress

Free radicals have been suggested to be involved in a number of disease processes. Recent studies (Russell et al. 2002) suggest that free radicals are involved in the development of cancer. The free radical theory of cancer suggests that there is a progressive decline in an organism's ability to resist free radicals reactions allowing irreversible tissue damage to occur. Regardless of their origin, it has been established that oxygen radicals represent a real threat to normal cellular function. Virtually all cellular components appear to be sensitive to radical/oxidant damage. Proteins, lipid, nucleic acids and carbohydrates are all known to undergo oxidative modification. The end result is dependent on the intensity of the oxidation stress and the capacity of the defences systems as well as the rate at which damaged bio molecules are removed. Decrease in oxidative repair may contribute to higher amounts of damaged macromolecules and ultimately to disease/cancer.

Cells are often exposed to high load of oxidants and free radicals. Oxidative stress can occur as a result of increased metabolic rate, increased oxygen tension, compromise of normal cellular antioxidants and many others endogenous and exogenous factors. Under normal conditions, the antioxidant defence systems are probably capable of maintain a low steady-state level of damage and thus protecting the cells. Among the risk factors for the development of prostate cancer are aging and life style. Under situations of oxidative stress and with increasing age, however, the organism may not be able to maintain homeostasis with deleterious and potentially unfortunate consequences. While it has not been conclusively determined whether free radicals are a cause or an effect of prostate cancer, it is clear that characteristic types of free radical damage increase with cancer. Free radicals are one of the environmental factors which contribute to cancer process.

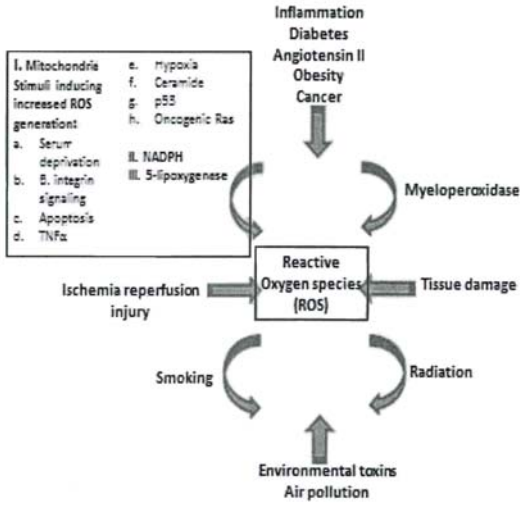


Figure 1. Cells are exposed to both endogenous and exogenous sources of reactive oxygen soecies (ROS)

Diet, Inflammation and prostate cancer

The causes of cancer have been largely attributed to genetic and environmental factors, including lifestyle, and are generally thought of as either avoidable or unavoidable. Dietary habits have been considered for years in epidemiological and case controlled studies to have an impact on cancer development and prevention. However, this association between diet and cancer has never been as clear as the correlation between smoking and cancer. Over nutrition, leading to obesity, has also been associated with increasing cancer development in many animal studies and is also considered a risk factor for many types of cancer (Johnson et al. 2007). Similarly calorie restriction appears to decrease risk for many cancers (Hursting et al. 2010). A major focus of diet and cancer research pertains to individual dietary components that may reduce or enhance cancer risk. Studying dietary components also gives more insight into the mechanisms involved in cancer development and how diet may play a role in modulating these mechanisms. There is an emerging consensus that situations of acute or chronic imbalance between the antioxidative capacity of cells and tissues, and the production of pro-oxidative species, is associated with the development of a number of human diseases. Despite enormous interest in the area of antioxidants as therapeutic tools, the development of foreign compounds as therapeutic antioxidants has provided little therapeutic benefit.

1 Many important physiological functions, such as the regulation of cell cycle (mitogenesis and apoptosis), are known to be tightly coupled to the induction of controlled episodes of oxidative stress in biological systems. This entails problems in terms of potential side effects for antioxidant therapy, which have been largely ignored in most clinical use of antioxidants. This may have serious implications for the choice of antioxidant principle to be used.

2 The actual choice of antioxidant therapy is it xenobiotic or endogenous, should be indicated based on sound molecular knowledge of the involvement of oxidative stress in the actual pathology.

Direct and indirect effects of diet and nutrition on cancer risk

The effect of diet can be direct, via the cumulative effect of exposure to nutrients and carcinogens in foods; in this case, the balance of cancer-promoting and -protective substances may contribute in defining cancer risk (Ahmad & Mukhtar, 2013). There are also indirect ways by which diet affects the cancer process. These include the effects of diet on energy balance and risk of obesity and the hormonal and metabolic responses related to energy balance. The latter are associated with

the metabolic syndrome and the inflammatory mediators linked to increased adipose tissue. In addition, diet as a determinant of growth and body composition may influence cancer risk both directly by affecting tissue growth itself and by affecting trophic hormones that mediate the growth process. Trophic hormones can influence the growth process and thus increase cancer risk. Obesity and rapid growth at critical times may increase the risk for some types of cancer; conversely, energy deficit and leanness may have a deleterious or protective effect for some cancers, depending on the timing or the tissue-specific effects of the nutritional deprivation (Parekh et al. 2012). Some infectious agents acquired through contaminated diets can affect cancer risk, such as chronic Helicobacter pylori infection, which induces inflammation of the gastric mucosa and thus affects cancer risk.

Antioxidant defence system

The human body contains a complex antioxidant defence system which depends on the dietary intake of antioxidants as well as the endogenous production of antioxidative compounds such as glutathione (Clarkson and Thompson, 2000; Majkowski et al. 2011). Antioxidants can act at different levels and by diverse mechanisms in the oxidative sequence (Halliwell & Gutteridge, 2007). Antioxidants can be classified into a number of different groups (Duarte and Lunec, 2005, Halliwell and Gutteridge, 2007):
1 Antioxidant enzymes: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GSR)
2 Antioxidative proteins: haemoglobin, ceruloplasrnine, transferrin, albumin, lactoferrin
3 Small-molecular-weight compounds: ascorbic acid (vitamin C), tocopherols (vitamin E), glutathione (GSH), uric acid, selenium, bilirubin, glucose
4 Ubiquinone (coenzyme Q_{10})
5 Flavonoids
6 Protein sulfhydryl (SH) groups (thiols)

The three major antioxidant enzymes are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx or GSH-Px). SOD and CAT are proteins which act primarily in the cell cytoplasm and form the first line defence against oxidants, e.g. superoxide anion and hydrogen peroxide (Gago-Dominguez and Castelao, 2006). SOD exists in several isoforms with different active metals in the center and different amino acid constituency. In humans, three different forms of SOD are cytosolic-CuZn-SOD, mitochondrial Mn-SOD, and extracellular SOD. Fe-SOD exists in animals but not in humans. Though CuZn-SOD is located in most parts of the cell, Mn-SOD is the most important scavenger of O-, converting it to hydrogen peroxide and oxygen (Halliwell, 2007).

Prostate cancer a search for etiologic, therapeutic, predictive and prophylactic factors

Carcinoma of the prostate (CaP) is still justly considered a hormone dependent disease but lacking curative treatments and a comprehensible aetiology. Several signs for adrenal involvement coupled with metabolic factors impelled this analysis on its aetiology. CaP seems to stem from a deficient production of two neuroendocrine components produced by adrenal zona-reticularis cells (ZR). One increase FSH, the other prolactin (PRL) levels which together control CaP. A curative ZR feed-back reaction can be activated in CaP patients by dietary supplementation compensating the aetiological metabolite deficiency (Tall berg et al. 2011; Crohns et al. 2013).

Natural components prescribed are; amino-acids serine (Ser), arginine (Arg); trace- element ions, strontium (Sr), vanadium (V) and molybden (Mo) in addition to ingestion of PSA-a serine

protease- levels may become stable or regress because the ingested substrate (L-Ser) causes enzyme inhibition, PSA-levels decrease. Gleason scores may decline from 8 to 4, paired with reduced urinary distress. CaP found incidentally, or by screening should primarily be treated utilizing dietary supplementation sine PSA may decrease in a dose-response manner, whereby serious side-effects caused by invasive treatments could be avoided. A good prognosis is usually registered as increased FSH, prolactin (PRL) and SHBG levels, declining DHEAS and PSA. Androgen ablation intervals' vary from 2-24 months, based on patient response permitting time for the adrenal feed-back reaction to function (registered as FSH increase). This bio-modulating schedule has been sustained already for decades (Tallberg & Atroshi, 2011) without emergence of a hormone refractory state (HRPC). A rare form of CaP is diagnosed from soft tissue metastases, with activin levels excessively increased, while inhibition stay low, but patients respond positively to this bio-modulating treatment. Orchiectomized patients have immeasurable inhibition, although normal activin levels as in pregnant females or ladies on oestrogen substitution therapy.

During intermittent LHRH treatment analogue treatment FSH is strived to be increased, over normal levels (>10 IU), with normal or increased PSA before the next hormone treatment is indicated. Androgen ablation should not attain a PSA nadir since excessive androgen suppression decrease FSH to low levels (<1 IU) when the adrenal feed-back cycle is exhausted, instigating HRPC. Fatal adrenal exhaustion is not due to pituitary dysfunction since PRL is then markedly increased in patients. There is a new incentive for screening since CaP can be arrested by non-invasive dietary means alone. Improved diagnostic serum markers; EPCA-2, Kinases, PSA velocity, MRI and constructive dietary trails should diminish the need for 12 biopsy cores as spread of malignant cells effecting recurrent CaP, already of >35% after prostatectomy. Gleason scores decreases, and bone metastases regress, albeit BPH may be activated requiring dutasteride medication, blocking 5a reductase I & II receptors.

Constrains linked to stem cell research, as compared with the refined medical regulation of cell induction caused by organ-specific mitochondria

The excitement generated by the recent approval of stem cell research in the USA, allowing the use of embryonic stem cells in humans may although, not form a ground-breaking new medical treatment modality. Stem cell research as it is scientifically performed today is constrained by specific limitations. These procured undifferentiated cells are not genetically identical with the recipient. After harvesting they must undergo manipulation by culturing in cell media. This may in a subtle way change their basic biological functions which is so essential for a truly physiologic prospective function in the new recipients' organ. The stem cell may not be introduced in the right inductional control segment exerted by the central nervous system (CNS). After cell culturing it may also be difficult to induce stem cells to function properly in a novel epigenetic milieu, especially if they have lost their organ specific mitochondria in the culturing process or during transfer of the stem cells to the recipient.

Introducing stem cells is like transplanting an organ and the recipient's immune system might reject the intruder. The toxic drugs required to prevent the immune rejection will not make it easier for the biologist to transform the surviving stem cells into their proper function, placed in a potentially hostile new surroundings. The sum of these scientific constrains originating from these vital but un-physiological preparative exploits will naturally delay clinical applications.

The “plasticity” of stem cells may lead to the use of a stem cell bank, but it would only partially circumvent transplantation problems, since storage could eliminate the essential organ specific mitochondria required for normal cell proliferation and transcription. A further serious complication is associated with malignant induction of teratomas, or any other malformed cell structures because stem cell induction is so complex that it is prone to turn into cell-structure despite our efforts to induce specific normal cell substitutes.

The source to obtain stem cells has varied a lot from embryos, placenta, amniotic membranes, umbilical cord cells etc. It is a way of circumventing killing an embryo but the cells are still potentially foreign when used as transplants. Unfertilized eggs have been chemically stimulated to create non-viable embryo cells with only one parent and less transplantation rejection potential, but may introduce other biological problems.

Organ-specific mitochondria utilized to create viable tissue cells, a novel scientific endeavour

The world's most promising new medical technology is introduced by the function of organ specific mitochondria. The human genome project revealed the surprising nucleotide analogy of chromosomes between different species. Mitochondria don't only produce energy for the nucleus, it has its shaped its chromosomal structure over eons of its phylogenetic toil. They regulate the healthy transcription of organ specific cells and can correct faults in the nucleotide sequences. Identical mutations present in both chromosomes, in Arabiodopsis plants, could lead to 10% of the offspring to be healthy. Mitochondria detected the nucleotide aberration and corrected the fault during regeneration (Lolle & Victor, 2005). Human "male" embryonal skin transplants could cause normal skin to develop in the bottom of the skin burn lesions. The skin formed was actually the girls own skin (Hohlfeld et al., 2005), and not caused by the male embryos skin transplants used. Organ specific mitochondria must be present in the embryonal skin.

These organ-specific mitochondria can transgress into the girls' tissue cells, and since they regulate the chromosomal genomes, which they have created during evolution-and of the girl's tissue cells can transform into skin, since the skin gene is present in any cell. The learning of the use of organ-specific mitochondria in biology and medicine will form the major scientific challenge for this coming century. The clinical use of mitochondria is not hampered by the same restrictions stem cells suffer from.

Oncothermia Journal 10:57-57 (2014)

Hyperthermia: Thermal Trap and Athermal Solution

Sergey Roussakow[1]
(1) General Director of Galenic Research Institute, Moscow (RUSSIA)

Since hyperthermia has still not become an accepted treatment in oncology despite of 50 years of intensive research, the problems of hyperthermia method should be detected and analyzed.

The current hyperthermia concept is based solely on the idea of temperature effect. The lowest acceptance of this temperature-based hyperthermia is caused by the lack of its effectiveness. This is still not recognized by hyperthermia community and is masked by so-called "successful" clinical trials, which are uniformly biased. In fact, the temperature-based hyperthermia is an "error-based" treatment. The fair and unbiased estimation of temperature-based hyperthermia problems is necessary for further development of the method.

Further development of hyperthermia is connected with refusal of "thermal dogma" as a key point of the hyperthermia concept. Non-thermal mechanisms of electromagnetic treatment should be an engine of the further development of the method. Ways to reach acceptance and specific features of hyperthermia trials are discussed.

Oncothermia Journal 10: 59-62 (2014)

Music Therapy In The Prevention And Treatment of Depression In Older Adults In lima-Peru

Segundo Armas Torres[1]

(1) Sociedad Peruana De Medicina Alternativa Y Complementaria, Miraflores, Lima, Peru

Music Therapy In The Prevention And Treatment of Depression In Older Adults In lima-Peru

Abstract

It is the first effort aimed at the application of Music Therapy techniques to help in the prevention and treatment of depression in the older person in the Miraflores of Lima, Peru. The Biopsychosocial and Yesavage tests were applied to all patients. We describe all the used techniques, the musical themes and therapeutic instruments used in a total of 50 people aged between 60 and 96 years, a six months treatment with a weekly frequency and culminated in a substantial improvement of problems like Depression, anxiety and nervousness as other mental health problems, among other achievements.

Keywords

Therapy, Depression, Elderly

"Music therapy is the first technique to approach the human being and also the last to join him". Dr. Rolando Benenzon

Definition

"Music therapy is a technique that allows the release (Catharsis) of psychological and organic pain related to improve the quality of life and revitalize"

"The Music therapy humanizes and dignifies elderly patient, and improve his quality of life"

Introduction

In Lima (Peru) there is a trend of population aging as a result of declining birth rates and rising life expectancy. It is estimated by 2014, people over 60 will represent close 15% of the national population. It has been estimated that the prevalence of lifetime depression is 20.4% in men and 19.6% in women with a very high frequency. Likewise, it calculated that up to 30% in people over 60 years have any of the various forms of depression. The presence of minor depression or subclinical depression is estimated at 35% to 40% of the older people and major depression in hospitalized patients with acute disease reaches 50%. It has been noted several contributing factors that could lead to depression in them: socioeconomic, family dynamics, retirement, isolation, violence, death of family and friends, financial loss, etc.

Theoretical framework

Music therapy with holistic therapy, which affects the totality of the human being is used in anti-aging medicine as part of the Mind-Body Therapy (TMC).

Dr. Rolando Omar Benenzon is an argentine music therapist, psychiatrist and researcher in this field, which has had different experiences in the use of music therapy, anti-aging medicine and depression. The proposed start treating the elderly, individually or in groups, after collecting a detailed history that relates to his personal history, and particularly to their taste and musical knowledge. The intervention was developed in three phases.

Phase I: Sound Life history
Phase II: Use of therapeutic musical instruments, songbooks, etc.
Phase III: Composition of songs and editing CDs

Features of music	Aspects to work with the patient
1. Capacity of evocation and recreation	Relieve depressive states
2. Ability to achieve relaxation and containment	Decrease anxiety. Promote muscle relaxation. Decrease pain perception.
3. Instrumental work	Expressing through instruments (object broker). Contain aggression / anger.
4. Creativity: Musical Instruments Workshops	Building self-esteem. Convert the subject in active patient.
5. Ability to communicate and socialize	Social Development, psychosocial and reduce isolation.

Theoretical background

In relation to the history, we made a thorough search of international literature among which are:
Effect of field experiences in music therapy: Choral Music Perception in Geriatric Wellness Programs. Journal of Music Therapy, Volume 41, Issue 4 (December 2009) pp. 340-352; Kimberly Van Weelden, PhD and Jennifer Whipple, PhD, MT -BC, of Florida State University.
Research conducted at the Cleveland Clinic in Ohio (2010), where Dr. Sandra L. Siedliecki, and a group of researchers found that when patients with chronic pain listened to music a daily hour for one week, their levels of pain, depression and disability decreased and were in the mood to improve depression.
Aitor Aitor Lorono L (2009) conducted a study with depressed people in BILBAO. They applied Music therapy to reduce depression and stress level using melodies that create an altered state of consciousness in which the person creatively overcome their conflicts and cause of their depression.
As for the effects of music therapy versus mood, there are an important number of researching, one of which is held in the school of medicine at Stanford University. The twenty men and women, aged 61 to 68 years old, who listened known pieces while practicing various stress reduction techniques without the help of a music therapist improved their mood and depression decreased them.

Objectives

Determine the effectiveness of music therapy in older patients with depression, anxiety and nervousness by applying the Biopsychosocial, Yesavage and modified Hamilton tests in patients in Lima, Peru. Also improving Self Esteem of older patients.

Materials and methods

Group composed of 50 (30 women and 20 men) from 60 to 96 years. None of the treatment group has had severe disorders; however, the majority had problems of depression, communication and family relationships, accompanied by feelings of loneliness, indifference, depression and aggression. From the physical point of view, there were disorders such as hypertension, diabetes mellitus, bronchial asthma and arthropathy.

Instruments

Clinical history and direct observation to rule out severe pathologies.
Yesavage Test. To quantify the geriatric depression scale.
Biopsychosocial Test. To pick up the fundamentals of psychological and physical measure was desired in the study.
Music Therapy Test (Musical History). To explore musical tastes and doing so in music therapy treatment for each patient.

Techniques

The patient is proposed to listening music according his personal taste, in order to stimulate the imagination and creativity and provoke memories, images and fantasies. Musical improvisation, as Bruccia model, involves spontaneously express freely and creatively through any musical instrument, the voice (singing) or body (dance). Travel Technical musical Cid (Posh 1999). Patient arises imaginary travel to various countries, helps the patient to escape recalling positive experiences and return to reality with a more positive spirit. Singing, either through musical improvisation described above or through musical dialogue. It consists of improvised music sequence exchanges between two or more people.

Dance therapy is to express through movement, rhythm, melodies or songs they hear or sing themselves. Schütz relaxation technique with musical background to achieve sedation states in the sessions, and also to teach individuals to use music application further use sedatives and individually.

Used music

Treatment included pieces of music of various genres, as Musical History of patients, most of whom chose classical music of Mozart, spiritual music church (The Lord is my strength, and how not to believe in God, the family hymn) and international music (ballads, Boleros, Clayderman, etc.). Also used dance music salsa, cumbias, etc. The musical themes were used: 1.- I BELIEVE IN GOD, 2.- IMAGINE, 3.- MOZART- K-448,4.- Resist 5.- HARMONY 6.- THE LORD IS MY STRENGTH 7.- DO NOT BELIEVE IN GOD AS 8.- FRIEND 9.- FAMILY, 10.-MY WAY

Procedure

The sessions, of one hour, is developed with a weekly frequency. The sessions comprised of active and passive techniques described above, with the understanding that the singing, playing, improvising and listening are musical activities that are used for therapeutic purposes and are determined by the individual characteristics manifest in previously conducted tests.

Methodology

The group consisted of 50 people (40 women and 10 men) from 60 to 96 years old, with an education that ranged from second grade to the upper level, with the following distribution: 04 university students, 06 high school (pre-university), 20 incomplete secondary, 20 primary education.

As psychological characteristics, although none had severe disorders, could be seen in most problems. Depression in varying degrees, as well as communication and relationship with the family, accompanied by feelings of loneliness, indifference, depression, aggression and few opportunities for recreation (all found from individual interviews and biopsychosocial test). From the physical point of view (as confirmed in the individual medical history), there were disorders such as hypertension, diabetes mellitus, bronchial asthma and arthropathy.

Results

Variables	Before treatment	After treatment
Depression	50	03
Loneliness	50	03
Sadness	50	02
Esteem	08	42
Aggression	15	03
Little communication	33	07
Disinterest	20	04
Nervousness	44	03
Socialization	10	42

Discussion of results

Music therapy is recuperative and preventive therapy that also achieving socialization, recovering the mood of patients, which means improving their self-esteem, strengthening their immune system and therefore the quality of their life.
The study case supports that the symptom categories benefit by 70% progress in improvements, which proves the effectiveness of the therapy in order to improve the quality of life in the population excluded by the system and even the family.

In a general sense could be seen that the work performed music therapy had a considerable impact on the elderly people who attended it. In fact, their mood improved visibly increased their family communication and social interaction, decreased their state of loneliness and alienation (common at this stage) and memory disorders and self esteem. It is interesting to note the enthusiasm with which this activity received, being that therapy time constituted an important time for them entertainment and distraction, in addition to connect with important experiences of his past.

As for the relationship between the clinical picture presented by patients and their ages, it did not found significant relationship while presenting diseases consistent with those suffering from the average of the patients, ie, hypertension, diabetes mellitus, arthropathy and depressive. However, and although there was no strict control over the experiment, reported a decrease in the amount of some medications used for relieving physical pain and sadness that characterized the beginning of it. Certain relationship was observed between the clinical and schooling, and that patients with higher levels of education facing the disease and seeking support mechanisms to live with more quality. This was evident from the start of the music therapy sessions to talk about their diseases and became more evident in the course of the same.

Conclusions

We conclude that Music is preventive and curative, especially for older patients with depression and other neurological diseases.

Although the sample was mostly women (as is common with psychotherapy groups voluntarily attending) which prevented meaningful comparisons between the sexes, as a trend was observed that from the physical point of view, both women and men, behaved very similarly, while that from the psychological point of view prevailed among women depressive symptoms.

This experience encouraged to continue its application and improvement in people of this age. The surrounding reality calls everyone to give them careful attention. In the final analysis, the law of nature dictates that all are born, grow, develop and die. Should be made by the actual older people the same what one would wish for himself in the future. It includes provide affection, attention, and not to deprive them of enjoying the most beautiful of the arts: Music. She is able to boot the hidden human feelings, as recognized by great musicians and arising the deepest emotions. It is fair to admit that "Love and music are the two wings of life and good health”.

Oncothermia Journal 10:64-67 (2014)

Hyperthermia in the management of head and neck cancer – A single institution study from India

Nagraj Huilgol[1], Sapna Gupta-Dutta[1], C. R. Sridhar[1]

(1) Department of Radiation, Oncology Dr. Balabhai Nanavati Hospital, S. V. Road, Vile Parle (W) Mumbai 400056, India

Hyperthermia in the management of head and neck cancer – A single institution study from India

Abstract

The addition of hyperthermia to chemo radiation or radiation can enhance the efficacy and increase disease free and overall survival. The review is the documentation of single institution study to assess the effects of hyperthermia in conjuction with radiation alone and chemo-radiation. This data has been published earlier. The retrospective analysis of patients receiving either paclitaxel or cisplatinum along with radical radiation and weekly hyperthermia did yield spectacular survival in advanced head and neck cancer. Similarly a randomized trial to assess the role of HT with radiation therapy has shown a statistically significant improvement.

Introduction

Head & neck cancers constitute a major burden of all cancers in men from India. There has been a trend towards a decline in oral cancer in a few major cities following a sustained campaign against tobacco consumption. Radiation and surgery alone have been supplanted by chemo-radiation laying an emphasis on organ preservation. Cyto toxic drugs and targeted therapies like cetuximab and nimatuzumab have been tried with success 43. Chemo-radiation or radiation with targeted therapies have come with a set of enhanced toxicities. But further improvement in survival with similar strategies in not very likely. Unfortunately addition of hyperthermia to radiation or chemo-radiation has not been pursued vigorously despite three randomized trials albeit sample size being small in these trials. S. Dutta, J. Valdagn, G. Huilgol. The present review documents data emanating from a single institution from India.

Material and methods

Hyperthermia facility was made available since 2003. A modified Thermatron was installed. It is a RF based machine which operates at 8.2 MH, the energy input varies from 0-1000 HW with impedance matching pre cooling and thermistors for online thermometry. A servo ensures an automatic shutdown if the temperature exceeds 50 °C. Three sets of antennae of different size ensure steezing of heat deposition. These is a dedicated head and neck antennae with a bolons for circulating cold water the temperature of which can be varied from 5° Celsius unless the tumor is just below the skin or skin is involved. Hyperthermia session lasts for 30-40 minutes. Thermometry is not done routinely but the energy inputs and values for impedance matching are recorded. Hyperthermia sessions are delivered on any of the days of radiation or on a weekend along with weekly chemotherapy. Patient also have been treated twice a week with adequate internal to account for thermal tolerance. Patients who were on chemo radiation besides hyperthermia receive either Cisplat or Paclitaxel, Cetuximab has been added to the armamentoteriom since last 4 years.

Patients with locally advanced head & neck cancers are routinely treated in our centre with both triple and dual modalities of CT+HT+RT, besides chemo radiation which is deemed a standard of care. An informed consent is a pre-requisite before starting any treatment. Patients who were recruited for the randomized trial, which was conducted from 2005 to 2009, were informed of the protocol before obtaining the informed consent.

Radiotherapy was delivered on a tele cobalt machine in the randomized trial. (Theratron 780C.). Patients treated after 2008 were treated on a linear accelerator with 6MV photons. Appropriate technique was adopted. Very few patients have been treated with intensity modulated radiation. Patients received 66-70 Gy in 6 to 7 weeks.

Hyperthermia was delivered on modified Thermatrom, a radiofrequency based machine which operates at 8.2 MHz. All patients underwent pre-cooling before starting chemotherapy only a few underwent invasive thermometry. The power input varied from 400 to 1000 k/w pain was the limiting factor for escalation of achieved to the extent possible.

Result

Patients were randomized to receive radiation therapy (RT) alone (control) or radiation with HT (trial). Twenty-six patients in the control group and 28 patients in the trial group were accrued. Table 1. shows demographic profile of both the group. The mean age of patients in the control group was 58.42 years (45-76 years) and in the trial group was 57.71 years (31-78 years). There was a male preponderance in both the groups. Both the groups were evenly matched with no statistical difference. Table 2. shows anatomical sub sites of affliction in both the groups. There was a non-significant preponderance of orpharyngeal cancers in the control group, while oropharyngeal and hypo pharyngeal cancers were slightly more in the trial group. Patients were saged according to Tumor Node Metastasis (TNM) system of stratification 1978 (UICC). Stage wise distribution is shown in Table 3. There is no significant difference in clinical parameters between both groups (Chi-square test, $p<0.05$=statistically significant). Patients in both the groups received radiation to total dose of 70 Gy in 7 weeks with conventional fractionation of 5 days a week with no treatment on weekends. Patients in the trial group received RF-based weekly HT in addition to RT. Twenty-one patients in the control group and 22 patients in the experimental arm received more than 60 Gy [Table 4]. Not all patients completed the planned number of sessions of HT. Twenty-three patients could finish more than five sessions [Table 5]. Those who dropped early were the ones who could not bear pain or the systemic stress.

Follow-up had been less than adequate in both the groups. The difference of follow-up pattern was not significant. Patients were assessed for any local recurrence, distant metastasis or development of new co-morbid illness not related to the original cancer at treatment. Both the groups were evenly matched for gender, stage, anatomical sites, treatment received and follow-up pattern. Initial response was assessed within 7-10 days of completion of treatment. The assessment of response was based on clinical assessment. Complete response was based on clinical assessment. Complete response was scored when total regression of the disease was seen, and partial response was scored when regression was more than 50% but not complete. Progressive disease was any increment in size of the tumor.
A complete response was observed in 11 of 26 (42.4%)
Patients in the radiation alone arm, while 22 of 28 (78.6%) patients had complete response in HT+RT group [Table 6]. Improvement in complete response due to addition of HT to radical radiation was statically significant (Chi-square test, $p< 0.05$). Three patient in RT+HT group and one patient in RT alone group had progressive disease. This difference was not statically significant. There were three details in the control group and five deaths in the trial group. Deaths were unrelated to treatment.

In RT+HT group, 3/28 (10.7%) showed progressive disease which was more than that in the RT alone group (1/26, 3.8%) but the difference was not statistically significant. Also, 17.9% subjects in RT+HT group were followed up for more than 12 months, which was more than (7.7%) that in the RT group, but was not statistically significant [Table 7]

Kalpan-Meir survival curve analysis showed a statistical benefit in those treated with RT+HT. The median survival of control arm was 145 days and mean survival time should median be rounded off to 203 days, 14-261. In trial group, median survival time was 241 days and mean survival time was (95% Cl) 260.471893 days (199.27426-321.669527 days). Median survival time is a better statistical tool to compare the treatment effectiveness.

The difference between the median times of survival between RT+HT and RT groups was almost 100 days. The survival function shows that the probability of survival was significantly different between the two groups. Except for a few days around 400, the survival function of RT+HT was the probability of death at any time was higher for patients treated with just RT. Cutaneous and mucosal toxicity in both the groups was comparable.

Parameters	**RT group**	**RT + HT group**
No. of cases	26	28
Age		
Mean	58.42 Years	57.71 Years
SD	11.39	12.93
Range		
Sex #		
Male	24 (92.3%)	22 (78.6%)
Female	02 (07.7%)	06 (21.4%)

P<0.05 significant

Table 1. Demographic data

Site	RT group (n=26)		RT+HT group (n=28)	
	No.	%	No.	%
Oropharynx	17	65.4	10	35.7
Hypopharynz	05	19.2	12	42.9
Oral cavity	04	15.4	06	21.4

By Chi-square test, P<0.05 significant

Table 2. Anatomical sites of head and neck cancer 1 control and trail groups

Response	RT group (n=26)		RT+HT group (n=28)	
	No.	%	No.	%
T2N0	01	03.8	01	03.6
T2N1	01	03.8	01	03.6
T2N3	02	07.7	02	07.1
T3N1	02	07.7	03	10.7
T3N3	04	15.4	04	14.3
T3N0	06	23.1	02	07.1

Table 3. Staging status in trial and control groups

T3N0	04	15.4	07	25.0
T4N0	-	-	03	10.7
T4N1	-	-	02	07.1
T4N2	02	07.7	02	07.1
T4N3	04	15.4	01	03.6

Table 4.

No of HT Treatment	No. of patients
2-4	2
5-7	23

Table 5. Profile of radiation dose 1 both the groups

Response	RT group (n=26)		RT+HT group (n=28)	
	No.	%	No.	%
Complete response	11	42.4	22	78.6
Partial response	13	50.0	03	10.7
No response	01	03.8	-	-
Progressive disease	01	03.8	03	10.7

Table 6. Comparison of response between two treatment groups

Duration (Months)	RT group (n=26)		RT+HT group (n=28)	
	No.	%	No.	%
<6	16	61.5	11	39.3
6-12	08	30.8	12	42.8
>12	02	07.7	05	17.9

Table 7. Profile of follow-up period

Discussion

There has been a considerable progress in the treatment of head and neck cancer. Chemo radiation as a standard of care has led to increase in organ sparing and maintaining functional integrity. This has come with on increased morbidity. Hyperthermia is a modality has been under utilized in the west as well as emerging countries including China and India. Hyperthermia that is raising the temperature to 41 °to 45° Celsius has unique mechanism of actions which is distinct from ionizing radiation and cytotoxic drugs. The biological rationale for the use of hyperthermia alone or as an adjuvant to radiation and chemotherapy are well known. Heat in the range 41 °to 45° Celsius affect various cellular targets like cell membrane Cyto Skelton and enzymes in respiratory chain.

Hyperthermia is very potent hypoxic cell senstiser. Thus hyperthermia in conjunction with radiation is an ideal combination to pursue. The present randomized study supported by Indian Council of Medical Research has shown a survival benefit for adding hyperthermia to radical radiation therapy. The median survival benefit of radiation therapy alone was 145 days as compared to 241 days in the HT+RT group.
A similar survival benefit was earlier demonstrated by Valdagin: (Similarly addition of hyperthermia to chemo radiation has shown excellent results. The morbidity due to addition hyperthermia was not significant in any of the patients. In conclusion both the randomized trial and the analysis of retrospective data demonstrate a significant improvement in survival due to the addition of hyperthermia.

Oncothermia Journal 10:69-70 (2014)

Hyperthermia in Cancer Treatment: Scientific Evidence in Clinical Experience

Alexander Herzog[1]
(1) Chief Physician of Fachklinik Dr. Herzog, Germany

Hyperthermia in Cancer Treatment: Scientific Evidence in Clinical Experience

Hyperthermia as anticancer treatment has been researched in the last decades and many mechanisms of action could be clarified. Investigations at the cellular level but also in animal experiments could show beneficial activity of the hyperthermia against cancer disease. Also in studies in human beings it could be shown that the activity of standard cancer treatments like radiation or chemotherapy could be enhanced by simultaneous hyperthermia.

So in Germany the private health insurances cover the cost of hyperthermia in conjunction with chemotherapy and radiation. However, in many countries hyperthermia is not used or not covered by the insurances claiming missing evidence for benefit.

Hyperthermia on its way to evidenced based medicine

In the medical scientific literature there are many studies about hyperthermia fulfilling the criteria of a critical assessment of validity and utility. However, the level of evidence is not the same for all tumor types. As for each type of tumor separately the proof of benefit of hyperthermia has to be shown the actual level of evidence depends on the studies performed up to now on specific cancer types. There also are differences using different devices or technologies of hyperthermia.

Hyperthermia and radiation in cancer of the cervix uteri

The combination of hyperthermia and radiation in cervical cancer belongs to the hyperthermia treatments mostly researched in randomized studies. In different studies it has been shown that performing hyperthermia in addition to radiation in advanced cervical cancer the rate of complete remissions could be increased from 57 % to 87% and the 3- years survival could be increased from 37 % to 51 % (Van de Zee et al, Lancet 2000). So in Holland this treatment combination is used as standard treatment for advanced cancer of the cervix. There is a picture what shows a patient with an advanced cancer of the cervix before and after combined local hyperthermia and radiation.

Hyperthermia in breast cancer

Also in a treatment of locally recurrent breast cancer there are studies showing benefit of local hyperthermia in combination with a second-line radiation. In a Meta-analysis of 5 studies using different techniques of hyperthermia it could been shown that the local tumor control could be improved by 35 % (Vernon et al, Int J. Radiat. 1996). Phase II studies showed a complete remission in up to 50 % of the cases (Bicher et al, Int. J. Radiat. Oncol. 1986). As in the situation of recurrent breast cancer the disease frequently is already systemic also whole body hyperthermia in combination with chemotherapy could be considered.
In an own small study in patients with metastatic breast cancer we achieved in 75 % of the cases a partial remission after whole body hyperthermia and chemotherapy (Herzog, Komplement, 2002).

Hyperthermia in ovarian cancer

Ovarian cancer is a tumor of the abdominal cavity. So local hyperthermia in these cases doesn't reach all abdominal tumors. More aggressive local approaches to treat the abdominal cavity with hyperthermia is the HIPEC treatment (hyperthermic intra- peritoneal chemotherapy).
In a study combining whole body hyperthermia with chemotherapy in the Dolphin Study from Munich successful results could be shown with a remission in 50 %and stable disease in 42% of the patients (Strobel et al, Dophin Studie, ASCO 2002).
There is a picture what shows an impressive case of an inoperable patient who we treated with whole body hyperthermia and chemotherapy (Carboplatin/Cyclophospharnid). The tumor masses

could be reduced down to a 5 mm remaining tumor in the left ovary which completely could be removed in a second look surgery. 5 years later the patient still is free of disease.

Hyperthermia in ENT-tumors

ENT-tumors frequently grow locally. They can be reached well using local hyperthermia. There are randomized studies showing an improved activity of a combination treatment of hyperthermia and radiation compared to radiation alone. Interestingly this mainly is valid for advanced stages. But also a combination of local hyperthermia and chemotherapy can be efficient in ENT-tumors. There is a picture what shows a patient who after several recurrences and pretreatments like radiochemotherapy and several surgeries a treatment combination of chemotherapy and local hyperthermia could achieve a complete remission lasting for 4 years. Also another patient with cervical lymph node metastases of a squamous cell cancer of the tonsil a combination of chemotherapy and local hyperthermia could achieve a lasting complete remission. This patient had refused radiation as she didn't want to go through radiation- induced side effects.

Hyperthermia in rectal cancer

There is one randomized study showing improved remission rates from 49 to 66% and prolonged time to recurrence from 20 to 28 months when a neoadjuvant radio-chemotherapy was combined with local hyperthermia (Rau et al, Schweiz. Rupdsch. Med. Prax. 2001). An own case report shows a patient who had suffered from a slowly growing rectal cancer for more than 7 years finally with penetration through the anus. After neoadjuvant radio-chemotherapy and local hyperthermia the tumor masses could be reduced that much that surgery could be performed finally maintaining a normal stool passage.

Hyperthermia in brain tumors

About the treatment of brain tumors with hyperthermia up to now there are no randomized studies available. But there are published case reports showing that also in these conditions a successful treatment is possible. In one of our cases, a patient with an advanced Oligodendroglioma grade II which had been progredient after several pre-treatments in an experimental approach combining regional chemoperfusion of the tumor (Prof Vogl, University hospital of Frankfurt) and local hyperthermia a surprising good response and disappearance of the symptoms could be achieved.

Evidence of hyperthermia

Considering the number and the quality of the published studies the level of evidence of hyperthermia treatment can be established (Image 8). Following the evidence criteria there is evidence level A for diseases like advanced cancer of the cervix uteri, recurrent breast cancer, esophagus cancer and ENT-tumors. According to the criteria of evidence there is a grade of recommendation A for the use of hyperthermia. For local recurrent rectal cancer, malignant melanoma and sarcomas there is at least one randomized controlled study. So also here the grad of evidence A may be assumed. In other tumors up to now there is no higher level of evidence but there is grade of recommendation B or C for the treatment with hyperthermia.

Conclusion

As conclusion can be stated, that the criteria of evidence based medicine for hyperthermia for several types of disease are fulfilled with high grade of recommendation as there are many randomized and not randomized studies. In other oncological diseases there are well documented positive case reports and experiences. In these diseases further research is necessary.

Oncothermia Journal 10:72-77 (2014)

Hormetic Effect of whole Body Hyperthermia (Experimental Study on Rats)

Nodar Mitagvaria[1], James (Haim) Bicher[2]
(1) I. Beritashvili Center for Experimental Biomedicine, Tbilisi, Georgia
(2) Bicher Cancer Institute, Los Angeles, California, USA

Hormetic Effect of whole Body Hyperthermia (Experimental Study on Rats)

It is established that hyperthermic exposure is associated with the development of oxidative stress in cells [Finkel, Holbrook, 2000]. The oxidative stress in its essence is related to the process of massive release of free radicals. The possible mechanisms responsible for the development of this process has not been sufficiently examined, although some of them are known. For example, activation of the immune system in response to infection when for elimination of microorganisms, phagocytes begin "shoot" by Hydrogen Peroxide (HP) - a strong oxidant.
It is known that the increase in resistance to oxidative stress is associated with the extension of the vitality of the body [Larsen, 1993]. In particular, it was found that low doses of oxidative stress (induced by, e.g., heat shock) slowing the aging process [Kurapti et al., 2000]. Practically here we have to deal with a phenomenon which is known as "Hormesis". This term originates from the ancient Greek and means "to bring in motion, prodding, acceleration". From a biomedical point of view the term "Hormesis" describes phenomena, when in response to low doses of toxins or any other stressors, the body develops a positive reaction (from a biological standpoint) - an adaptive stress-response, which provide stability of cells to higher (fatal) doses of stressogenic factors stimulating the response (Calabrese et al, 2010).
In recent years the interest to the phenomenon of hormesis has increased enormously, because stress can be physical and chemical, as well as psychological. Even the radiation hormesis, i.e. protective effect of low doses radiactive exposure is under intensive investigation.
The main purpose of this study was to investigate the effects of oxidative stress caused by Whole Body Hyperthermia (WBH) on the behavior of white rats. It should be noted that during the formation of this goal, we did not assume any connection with the phenomenon of hormesis, but the results have forced us to delve into the essence of this particular phenomenon.
For the purpose of comparative evaluation of received results, we found it necessary to use also another method of inducing oxidative stress – chronic administration of HP.

Materials and methods

The experiments were conducted on seven groups of white rats weighing 250-300g (both males and females). State of oxidative stress in animals (before their testing in a multi-way maze) was caused either by WBH or by administration of HP. In particular:

1. The first group of rats instead of regular drinking water for four weeks were allowed to 0.1% solution of HP. We used food-grade HP (Wellness, 35% H_20_2); since the beginning of the fifth week the animals began to be trained in the maze for learning the optimal trajectory to get into the nest-box. Prior to the completion of testing (7-8 days), rats, instead of regular drinking water continued to take a 0.1% solution of HP.
2 The second group of rats exposed to WBH in a special hyperthermic chamber. The temperature in the chamber was maintained at the level necessary to achieve a rectal temperature of 40 °C, and this level was maintained for 4 hours. This kind of exposure they received every other day for four weeks. After completion of all hyperthermic exposures, the animals ofthis group were also tested in a multi-way maze.
3 The third group of rats received a combined dose of stress: daily receiving 0.1% HP with drinking water for 4 weeks (similarly to the first group) and every other day the animals were also subjected to WBH, similarly to the second group of animals. Then, the animals of this group were tested in the multi-way maze.

4 A fourth group of rats 15-20 minutes before of each hyperthermic exposure received an intraperitoneal injection (30mg/kg) of a nonselective inhibitor of nitric oxide synthases (NOS) - Nitro-L-Arginine Methyl Ester (L-NAME); After these actions animals of this group were also tested in the maze

5 The animals of the fifth group 15-20 minutes before the beginning of the daily maze sessions, similarly to the fourth group of animals, received an injection of non-selective inhibitor of NOS - L-NAME, but animals of this group were not subjected to WBH.

6 The sixth group consisted of animals, which 15-20 minutes before the start of the daily maze sessions, opposed to the fifth group received an injection of selective inhibitor of inducible nitric oxide synthase (iNOS) Aminoguanidine at a dose of 30 mg/kg.

7 The control group were intact animals, not exposed neither to stressogenic nor pharmacologic factors. A general view of the maze that we used is shown in Figure 1.

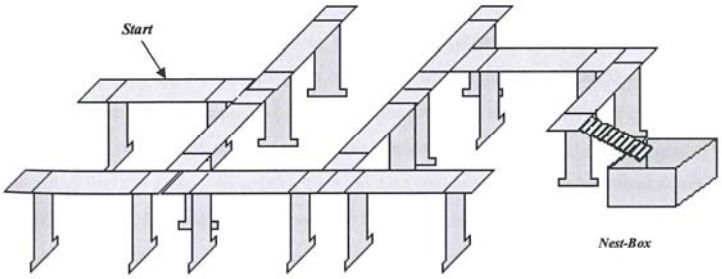


Figure 1.

It consists of separate bridges (30 cm high), which makes it possible to easily change the configuration, complicate or simplify the task - getting into the nest-box. At the first start of animals through the maze (the first day of the maze session), experimenter usually helps animal in finding the optimal trajectory from a start to destination point (nest-box), and later they learn independently, by trial and error. The experiments were carried out without food reward, the incentive to move through the maze is the getting rid of not ethological situation - being on the maze platforms. Conditions in the experimental room (lighting, location of objects, etc.) until the completion of the experiments remained strictly unchanged. Assessment of testing is carried out for the two indicators - the number of errors committed (deviations from the optimal trajectory) and the time spent for the passage from start point to the nest-box. Registration of the named indices starts from the second day of training, so as in the first day of the majority of the animals received assistance from the experimenter. At the end of experiments from each experimental group two animals were randomly selected for a blood test (analysis of rheological properties), and two more for morphometric studies of the sensorimotor cortex (the results of these studies will be discussed in a separate article).

Results

From the very beginning of analysis of the received data we have to underline that no statistically significant differences in maze learning from the point of view of reducing the number of errors (deviations from the optimal trajectory) in between of groups has not been observed. On the seventh day of training (five starts per day) almost all of the animals were able to pass a maze without a single error, but if we compare the time spent for maze passage differences have been identified in between of different groups.

Figure 2. Shows the change of time required for passage of the maze by the different groups of animals. In particular, there are the control group and the groups that underwent oxidative stress by

administration of HP or WBH, as well as the group that received combined action of both stress factors.

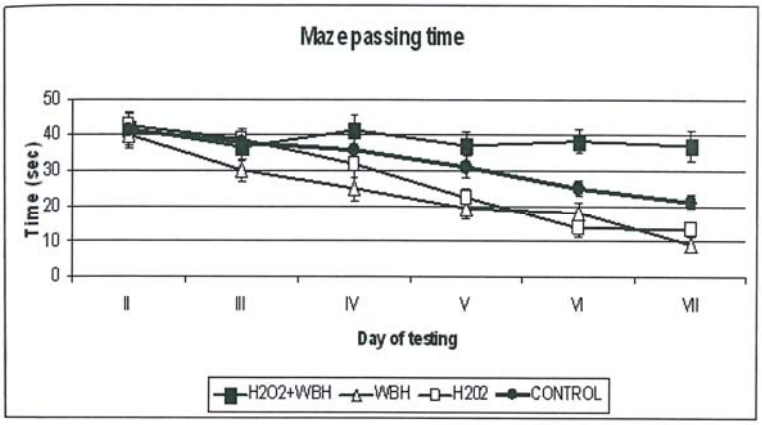


Figure 2.

Figure 2. Time required for passage of the maze by the control group and the groups that underwent oxidative stress by administration of H_20_2 or by WBH, as well as the group that received combined action of both stress factors.

It was found that animals that were exposed to stressors either chronic administration of HP or WBH, significantly increased their behavioral activity. In comparison with the control animals they behaved on the maze platforms very lively and energetic, and at the end of the seven day training, they were able unmistakably pass all the way almost twice as fast as the control animals (Fig. 2)

In contrast to first two groups, the animals from the third one, that received the combined action of both WBH and HP, dramatically slowed the behavioral activity, animals looked depressed and to achieve the final target at the end of the seventh day of the maze sessions, the needed time two times greater than the control animals and three times more than the group that underwent the action by one of stress-factors.

As indicated in the methodical part of this paper we also had other groups of animals. In one of them (fourth group) the animals every day (in duration of four weeks) were administered by L-NAME, and besides, they every other day underwent the WBH. Testing of animals from this group in maze showed that time for maze passage does not differ from that observed in animals that were exposed only WBH, or those that have taken just HP solution (Figure 3, curve with open triangles).

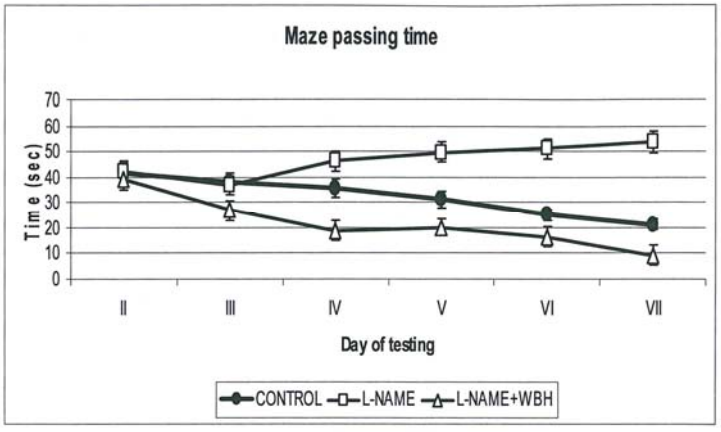


Figure 3. Time required for passage of the maze by the control group, the groups that underwent L-NAME administration and the group that received combined action of L-NAME and WBH

The animals of fifth group prior to maze sessions were administered by NOS nonselective inhibitor - Nitro-L-Arginine Methyl Ester - L-NAME (30 mg/kg), but unlike the previous group animals did not get the hyperthermic exposure. As can be seen from Figure 3 the motor activity of the animals in this group declined sharply and at the end of training sessions (7th day) the animals were able to reach the nest-box on average for 55 seconds, which is more than twice greater than the time spent on solving the same problem by animals of control group.

To assess the role of Nitric Oxide, produced by activation of its inducible synthase (iNOS) special (sixth) group of animals instead of L-NAME were administered by selective inhibitor of inducible NOS - Aminoguanidine (30 mg/kg). In this group of animals a statistically significant difference in time needed to pass the maze in comparison with the control group were not revealed (see Figure 4).

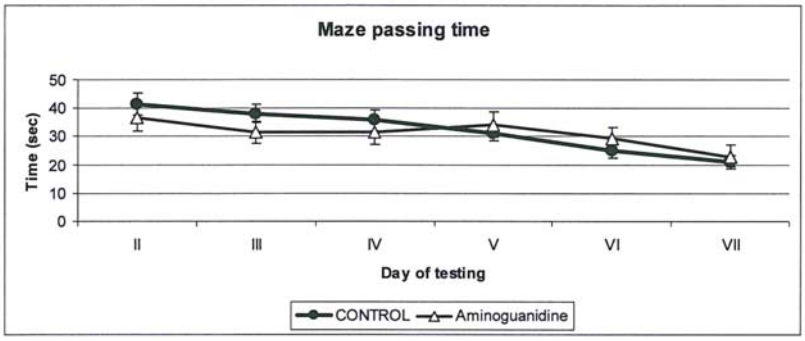


Figure 4. Time required for passage of the maze by the control group, the group that underwent Aminoguanidine administration

Despite the described differences in time of the maze passage, as we have already mentioned above, statistically significant difference in the number of errors committed in the process of learning between used groups of animals have not been identified. The learning process in accordance with this criterion in all groups of animals was almost the same.

Discussion

The body's resistance to stresses is one of the most important indicators of its viability and it is clear that the study of the mechanisms that shape this resistance have a fundamentally important character (Michalski, Novoseltsev, 2005).

Oxidative stress, as noted, is involved in the development of many pathological processes (Nunomura et al., 2005; Ramalingam, Kim, 2012; Singh et al., 1995; Valko et al, 2007), but it appears that it may play a significant role in processes of physiological adaptation and regulation of intracellular signal transduction. It is believed that the most appropriate definition of oxidative stress is a "state in which oxidation exceeds the antioxydant systems in the body secondary to a loss of balance between them" (Yoshikawa, Naito, 2002).
Markers that may help in the recognition of oxidative stress in in-vivo conditions are gaining in importance, because the determination of the state of oxidative stress is essential not just for the study of many diseases, but also to improve the efficiency of their treatment (Yoshikawa, Naito, 2002).

The above mentioned proves that for the study of oxidative stress problems it is essential to have an adequate experimental models. To these kind of models can be confidently attributed the

chronic administration of HP (0.1% in drinking water) or the use of whole-body hyperthermia (heat shock), which were used in our work.
There are suggestions that chronic stress can contribute to disorders of learning and memory, and that it is an important contributor in the development of Alzheimer's disease (Nunomura et al., 2005; Jeong et al., 2006). According to the theory of D. Harman (1956, 1972), oxidative stress plays a significant role in the processes of aging. Further development of this theory oddly enough, got in the works, which argue that free radicals may contribute significantly to metabolic health and life expectancy (Ristow, Schneisser, 2011; Guliano, Watson, 2012). This effect is known as mitochondrial hormesis (mitohormesis).

The aging process is associated with a stochastic accumulation of damage at the molecular level and progression of inability to restore them. The use of the phenomenon of hormesis in the study of this process is based on the principle of stimulation of recovery processes by use of repeated exposure to mid-level stress. One of the first versions of this methodical approach was the use of repeated thermal shocks on the culture of human cells. The results of these studies have shown that the use of the principle of hormesis in gerontological research has a very promising future (Rattan, 2005). By activating the stress responses at the cellular level Mattson (Mattson, 2005) concluded that the organisms that in the process of evolution used the toxic agents from the environment to their advantage, often used them as signaling molecules that trigger adaptive stress responses. Examples are nitric oxide (NO) and carbon monoxide (CO), amino acids (e.g. glutamate) and ions of Ca and K.

Analyzing the mechanisms of HP-induced oxidative stress in in-vitro models, Coyle (2004) came to the conclusion that in its development involved the nitric oxide synthase (NOS) and NADPH-oxidase, which, in fact, serve as a source for increased level of reactive oxygen species. The presence of cytoprotective properties of the responses to stressors caused a widespread interest in the creation of pharmacological agents capable of inducing stress reaction, but their level should not go beyond the hormetic reactions.

The fundamental basis for understanding the phenomenon of hormesis curve is the "dose-response", which shows the process of stimulation at lower doses and inhibition - at high.
Low or high doses of stress factors cause, respectively, eustress or strong distress, resulting in activation of moderate or damaging allostatic buffering capacity of the organism. This is true no matter what the nature of the stressor is - the physical, chemical or mental (Cornelius et al., 2013). These authors believe that a well-known concept of preconditioning is a classic manifestation of the phenomenon of hormesis.

On the background of all foregoing, analysis of our results allows to conclude that in our experiments, we observed behavioral manifestations of the phenomenon of hormesis. A very significant increase in behavioral activity aimed at getting rid of from non ethological conditions in response to oxidative stress caused by the introduction of HP (the first group) or hyperthermic exposure (second group), in our opinion indicates that in both cases the dose of induced stress was within the range needed for stimulation of hormetic mechanisms.

Combined exposure of both stressogenic factors (WBH and HP) have apparently brought to the level that is out of functioning of hormetic mechanisms. Roughly similar results were obtained earlier in drosophilas, flying speed of which after application of oxidative stress by HP, was, according to the authors, "dramatically increased» (Grover et al., 2009). And two years earlier than Grover et al, again in Drosophila has been shown that hyperthermic preconditioning (36°C for one hour) improves the locomotor activity (Xiao et al., 2007). In addition, it was found that low dose stress increased also life expectancy of Drosophila (Butov et al., 2001). It is believed that this effect is due to activation of heat shock proteins chaperone functions, resulting in not only in reparation of damage inflicted by stress, but also that having place before applying the exposure of

stressor (Butov et al., 2001). Operation of this mechanism is generally associated with the production of nitric oxide (Romano et al., 2011).

In our experiments, inhibition of production of nitric oxide in the group of animals that hyperthermic exposure was carried out on the background of the non-selective inhibitor of NOS-L-NAME, as we can see on Figure 3, practically there is not any changes in hormetic effect of hyperthermic stress. The same figure clearly demonstrates that in normal animals (without stress exposure), blocking the production of nitric oxide, as compared with the control group, and even more with the group in which against the background of the NOS non selective inhibition was subjected to hyperthermic stress, significantly decreased locomotor activity of animals.

In according to data obtained from the next group of animals, we can conclude that the sharp decrease in locomotor activity on the background of L-NAME, was mediated by inhibition of endothelial isoform of NOS. Figure 4. clearly shows that the selective inhibition of the inducible isoform of NOS by Aminoguanidine, almost did not have any effect on the behavior of rats in a maze – a statistically significant difference from control animals were not detected. It is possible that in the case of non-selective inhibition of NOS, hyperthermic exposure activates another source of oxygen radicals, namely NADPH oxidase (Coyle, 2004) which provides the formation of oxidative stress and induction of hormetic effect.

Anyway, we think that the results of our experiments suggest that for the formation of oxidative stress and accordingly hormetic effect, the presence of nitric oxide is not a necessary factor, at least in case of oxidative stress caused by WBH.

In this presentation, we did not consider such important issues as the activation of the transcription factor Nrf2, as well as the system of heat shock proteins, which without any doubts are involved in the formation of hormetic effect caused by WBH.

Oncothermia Journal 10:78-78 (2014)

Thermography controlled wIRA-hyperthermia & Low Dose Re-Irradiation in Recurrent Breast Cancer

Notter M.[1]
(1) HNE Service de Radiothérapie, CH 2300 La Chaux-de-Fonds, Switzerland

Abstract
In combination with low dose radiotherapy, superficial hyperthermia offers the possibility of achieving local control in previously irradiated recurrent breast cancers. Technially, this requires the ability to control temperature distribution in the heated tissue, to adapt heat application to changes in tumor volume, to avoid overheating of normal tissues and to minimize the risk of burns. Our clinical experience of combined hyperthermia-radiotherapy treatments using thermographic monitoring and control in chest wall recurrences is presented.

Keywords
wIRA hyperthermia, breast cancer

Methods
Infrared radiation was applied using a commercial wIRA radiator (hydrosun ®750). Temperature distribution in the treated region was monitored continuously by an infrared thermography camera (VarioCAM® high resolution Jenoptik) mounted to the wIRA radiator and remotely controlled by a computer. Specialized software (Heatcontrol®, InfraMedic) was used to keep skin and tumor temperatures constant, whereby a measurement ROI and minimum and maximum temperature values (41-43^{o}C) were selected. Visual inspection of the temperature color-coded images was additionally used for guidance in the correct centering of the heated region and to avoid hot spots. After 45-60 minutes of hyperthermia, re-irradiation was applied with 4-8 MeV-electrons within 1-5 minutes. Hypofractionated RT consisted of 4-6 x 4 Gy 1x/week, up to a total dose of 16-24 Gy.

Results
From 9/2009 to 9/2013, 63 heavily pre-irradiated patients with locally advanced recurrent breast cancer were included in the study. Tumor nodules generally achieved the prescribed maximum skin temperature of 42.5 – 43.2^{o}C with minimum temperatures of 41.5 – 42.2^{o}C. The displayed video thermographs allowed dynamic adaption of the appropriate area of heat applications to subsequent electron irradiation by localizing tumor nodules, cold and hot spots, scars and hyperpigmentation, relative to visible or palpable skin structures. Treatment response was evaluated clinically by MRI and/or PET-CT. 64% CR, 30% PR, 4% NC and 2% PD of 97 treated volumes was achieved. The combined treatments were well-tolerated.

Conclusions
Use of thermography-controlled wIRA-hyperthermia combined with low dose re-irradiation provides good local control of heavily pretreated chest wall recurrences. Dynamic thermography imaging provides not only safe control of heating but also reveals fine details concerning the physiological response to heat absorption. Changes is the on-off heating frequency pattern during hyperthermia have been observed and could provide vascular decompression parameters through model analysis. The remissions achieved so far are very promising and correspond to results found in the literature. This study demonstrates for the first time the possibility of a real-time, online monitoring and control of local superficial hyperthermia all over the whole treatment field.

The 32nd Annual Conference of the International Clinical Hyperthermia Society (ICHS)

ICHS Conference Papers

Usage of Booster in different conditions

Dr. Hegyi Gabriella MD. PhD[1], Dr. Csütörtöki Krisztina MD[1], Dr. Pfeiffenróth Anna MD[1]

(1) Pecs University, Health Science Faculty, Hungary

Introduce

The use of the Booster in oncology can help to increase the action of both chemotherapy and other drugs. It can be used with all common cytostatics regardless whether these are administered orally, intravenously, rectally, inhaled or percutaneously. The Booster can be used for treating all types of cancer. The only limitation is the size of the electrodes. The treatment of metastases is also difficult. The Booster, which is the latest development from Oncotherm, was developed for oncology but can nevertheless also be successfully used in other medical fields. In addition to oncology, it can be used in fields such as rheumatology, sports medicine, neurology and neurosurgery, dermatology and analgesic therapy.

Method and procedure

We tried to treat and stop development of Dupuytren's contracture (also known as morbus Dupuytren, Dupuytren's disease or palmar fibromatosis) is a fixed flexion contracture of the hand where the fingers bend towards the palm and cannot be fully extended (straightened). It is an inherited proliferative connective tissue disorder which involves the palmar fascia of the hand. Selecting patients and working with a special protocol for each of them 3 times a week for 1 month, with repetition 2-3 times according to investigation. We treated patients in contracture stage I-II.

Results

According to physical investigation and personal experience we can advise Booster-treatment for this disease as a newer indication completing physiotherapy.

Discussion

The increased temperature also regulates the cell cycle by changing the calcium ion binding. In addition, the following effects in the blood and tissue can also be achieved:

- Increased fibroblast activity and increased capillary growth
- Increased nutrient concentration and metabolic activity
- Synergetic increase in the field-dependent effects (optimization of membrane stimulation and activation of signal channels etc.)

Keywords

Booster, oncothermia, connective tissue, Dupuytren's disease, alternative treatment

Early Clinical Experiences of Oncothermia in Locally Advanced Non-Small Cell Lung Cancer

Chang Geol Lee M.D.[1], Yang Gun Suh M.D.[1], Ji Hye Cha M.D.[1], Jao Ho Cho M.D.[1], Youn Han Lee Ph.D.[1]

(1) Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea

Purpose

To evaluate early clinical outcome of Oncothermia combined with concurrent radiotherapy (RT) and/or chemotherapy (CTx) in locally advanced non-small cell lung cancer (NSCLC).

Materials and Methods

Since the introduction of Oncothermia (EHY-2000) machine at Yonsei Cancer Center in June 2012, a total of ten patients with locally advanced NSCLC were treated definitively with Oncothermia combined with concurrent RT and/or CTx-RT at Yonsei Cancer Center. The median age was 64 years (range 45-83 years), and all were male. The distribution of stage were 1 stage II, 2 stage IIIA, and 7 stage IIIB. Oncothermia was applied 2-3 timers a week, 60 min/session. Mean total treatment session was 11 (range 10-12 sessions). The applied forwarded power was 100-10 W depending on the personal tolerance of the patients. Oncothermai was administered concomitantly with RT in 4 patients (OR group), with concurrent CTx-RT in 6 patients (OCR group). Median RT dose was 63 Gy (50-60Gy/5-7 wks). Concurrent CTx using Taxol/Carboplatin was administered 2 cycles during RT. Treatment response was evaluated with CT or MRI within three month after the last session of Oncothermia, using WHO criteria.

Results

Oncothermia was tolerated well in all patients, and no patient suffered significant side effects including fat necrosis, burn, and skin reaction. Complete response (CR) and partial response (PR) were observed in 2 (20%) and 8 (80%), respectively. Treatment response for each treatment group was: CR ¼ (25%) and PR ¾ (65%) for OR group; CR 1/6 (17%), PR 5/6 (83%) for OCR group.

Conclusion

Although the study was limited by small number of patients and short follow-up, we were able to show that oncothermia concomitantly with RT or CTx-RT resulted in significant response for locally advanced NSCLC without any adding side effects. We will continue follow-up and evaluate the efficacy of Oncothermia.

What are the trends in local hyperthermia?

Dr. Oliver Szasz, PhD, assoc. professor[1]
(1) Biotechnics Department, St. Istvan University, Hungary

Introduction

Hyperthermia was one of the very first medical approaches. It was based on various religions and had deep philosophical roots in most of the ancient cultures. The discovery of electromagnetism gave new hopes for oncological applications a century ago, however up to now it suffers from lack of wide acceptance.

Medical challenges

The main problematic points of the extended applications are connected with the control of the process, the adequate dose and protocol of the method and the reproducibility of the results. Hyperthermia in oncology has similar status that other medicaments, the difference between the medicine and poison is only the dose. The other medical challenge is the systemic, non-local effect of the malignancy, which is curatively approached by a local method. This is of course a (apparent) contradiction, which has to be solved for further developments.

Biological challenges

Hyperthermia struggles the dose problem above, and sometimes it hinders the biological factors. However, the applied heating has definite consequences: the physiologic control of the human body tries to compensate the active deviation from the homeostatic equilibrium. The compensation is the higher blood-flow in the heated volume, which delivers nutrients (mainly glucose) to the tumor as well as increases the risk of metastases.

Technical challenges

There are numerous electromagnetic hyperthermia methods applied. These are distinguished by the kind of the fields, frequencies, heated volume, and conjunction with other methods, etc. The main problem with the various technical solutions is the loss of the basic control over the processes in depth of the body. The methods became increasingly sophisticated to keep the deep-heating controlled.

Answers on the challenges

A proper technical and physiological solution is necessary to be harmonized with the overall and local feedbacks of the complex living system. Clues for the success of the proper hyperthermia treatment are: (1) accurately select the tumor; (2) do not excite the homeostatic correction feedbacks (like blood-flow); (3) select properly the malignant cells; (4) use effective cell-killing for the malignant cells; (4) act on innate and adaptive immune system completing the job. The solution of making selected concentration of the electromagnetic energy on the sensitive points of malignant cells is the nanoscopic heating. This method is popularly called oncothermia. Solving the non-locality problem of the malignancy is in the center of the nowadays research. Oncothermia is devoted to solve this point, having multiple laboratory and clinical results providing answer. The clue is the immune supportive treatment, which is realized in abscopal (bystander) effect. Synergy with the well-known systemic approaches like traditional Chinese medicine (TCM) is naturally offered, and the results on this line are very promising.

Conclusion

Oncothermia is a selective and effective method. It is a vivid way solving the old-problems in hyperthermic oncology: it is a controlled, reproducible and reliable treatment. Its abscopal effect and wide synergy possibilities with TCM opens a new renewal of hyperthermic oncology.

Oncothermia Journal 10:84-89 (2014)

Percutaneous CT-guided radiofrequency ablation for unresectable hepatocellular carcinoma pulmonary metastases

Xishan Li[1], Jianpeng Wang[2], Wang Li[1], Zilin Huang[1], Weijun Fan[1], Yumin Chen[1], Lijie Shen[1], Tao Pan[1], Peihong Wu[1], Ming Zhao[1]

(1) Minimally Invasive Interventional Division, Medical Imaging Centre, State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Centre, Guangzhou, China

(2) Target and Interventional Therapy Department of Oncology, First People's Hospital of Foshan, Affiliated Foshan Hospital of Sun Yat-Sen University, Foshan, China

Percutaneous CT-guided radiofrequency ablation for unresectable hepatocellular carcinoma pulmonary metastases

Purpose

To evaluate the outcomes of percutaneous CT-guided radiofrequency ablation (RFA) for unresectable hepatocellular carcinoma pulmonary metastases (HCCPM) and to identify the prognostic factors for survival.

Materials and methods

320 patients with pathologically or clinically confirmed HCCPM between January 2005 and January 2012 were reviewed. 29 unresectable candidates (26 men and 3 women) with 58 HCCPM were treated with 51 percutaneous CT-guided RFA sessions. The outcomes, including safety, local efficacy, survival and prognostic factors were evaluated.

Results

Pneumothorax requiring chest tube placement occurred in 2 (3.9%, 2/51) RFA sessions. During the median follow-up period after initial lung RFA of 62 months (range, 5-75 months), 18 (62%, 18/29) patients died of intrahepatic tumor progression and 11 (38%, 11/29) patients still alive. The 1-, 3- and 5-year overall survival rates from initial lung RFA were 71.6%, 27.9% and 9.3%, with the median survival time was 26.3 months (range, 3-66) in all patients. Univariate and multivariate analysis revealed serum AFP level small than 400ng/mL and complete response rate after initial lung RFA as better prognostic factors for overall survival.

Conclusions

As an alternative treatment procedure to pulmonary metastasectomy, percutaneous CT-guided RFA can be a safe and effective therapeutic option for unresectable HCCPM patients.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumors worldwide and the third contributor to cancer-related death. With the advancements of the multidisciplinary application of the surgical resection, transplantation, radiofrequency ablation (RFA), and transcatheter arterial chemoembolization (TACE), the intrahepatic tumor has been well controlled and the survival has been gradually improved, however, the prognosis of patients with extrahepatic metastases remains poor with the median natural survival time after diagnosis of extrahepatic metastasis was only 7-8.1 months. The lung is a prime metastatic target organ with approximately 20-30% of advanced HCC experienced pulmonary metastasis synchronously or metachronously. Lung metastasectomy has been validated as the curative therapeutic option to solitary pulmonary metastatic patients. However, only 25-30% of highly selective HCCPM patients benefit from surgical resection because of the association of multiple lung metastases or extrapulmonary disease. In addition, a trend of early recurrence and/or new metastatic lesions after lung metastasectomy also limits the second lung surgical indication.

Other alternatives palliative therapies in unresectable HCCPM are radiation therapy, alone or combined with systemic chemotherapy, but these therapeutic options have not greatly improved patient prognosis. New targeted agents such as sorafenib have been shown to extend survival in selected advanced HCC patients, however, a recently prospective phase II trial indicated that the presence of lung metastasis predicted poor response to sorafenib in advanced HCC patients.

Therefore, a novel therapeutic strategy is required to improve the survival of patients with unresectable HCCPM.

RFA has been accepted as a relatively safe and useful therapeutic option in the treatment of selected primary and metastatic lung tumors. The advantages of satisfied local control rate, repeatability, minimal invasion with short hospital stay and gain in quality of life, suggesting that RFA might be an alternative option for HCCPM patients where lung metastasectomy is unfeasible. Moreover, some studies have shown clinical outcomes of lung RFA in controlling HCCPM, however, the survival benefit of RFA as an either additional or substitutive local treatment method is still lacking in the pursuing of treatment in HCCPM and it remains to be determined whether survival data were a simple reflection of natural history in such a population. So in this study, we presented our experience on unresectable HCCPM patients characterized by adequately controlled intrahepatic lesions and no extrathoracic metastases, treated exclusively with lung RFA. The complications, local efficacy, survival and prognostic factors were evaluated which may be useful in cumulating evidence of this practice in HCCPM. The time interval between diagnoses of the HCC and lung metastases, number of tumors, and size of the largest tumor, hepatic virus infection, ZPS, serum AFP level before initial lung RFA, the response after initial lung RFA were assessed for its effect on survival.

Materials and methods

The retrospective study was approved by our institutional review board, and all patients provided written informed consent before CT-guided RFA for HCCPM.

Patient selection

Between January 2005 and January 2012, 320 consecutive patients without any evidence of distant metastases other than lung were reviewed. 29 unresectable candidates with 58 HCCPM were treated with 51 percutaneous CT-guided RFA sessions. There were 26 men and 3 women with a mean age of 49.6 years (range, 24-72 years). All patients treated with RFA had lesions proven to be pulmonary-only metastases from HCC based on typical radiological features of HCCPM on CT/MRI or PET-CT with the history of HCC, except for 3 patients who underwent CT-guided lung biopsy before RFA as the presentation is atypical.
The intrahepatic tumor was controlled by hepatectomy+TACE+RFA (n=I0), liver transplantation+TACE+RFA (n=9), RFA (n=3), TACE+RFA (n=7), and the results were evaluated by CT scans with a contrast medium after one month later. The mean number of lung metastases was 2 (range, 1-8) and the maximum diameter was 17.5 mm (range, 5-50 mm) at the time of initial lung RFA. The mean disease-free interval between the time of the diagnosis of HCC and development of lung metastases was 17.7 months (range, 1-85 months). The mean duration between appearance of lung metastases and RFA was 6 months (range, 0-38 months). The last day of follow-up ended on the date of death or January 31 th, 2012, and the median follow-up period was 62 months (range, 5-7 months).

Preablation evaluation

The evaluation of intrahepatic tumor being "controlled" was based on radiological images without intrahepatic enhanced lesion lasting for more than one month after the curable treatment or along with the normalization of serum AFP for asynchronous metastases. For patients with synchronous lung metastases, the preferred treatment of intrahepatic lesions with curable intent was performed.

The judgment of lung metastases being "unresectable" and the indication for RFA were made by an interdisciplinary tumor board consist of thoracic surgeons, hepatobiliary surgeons, medical oncologists, radiation oncologists, and interventional radiologist taking the number and distribution of the lung metastatic lesions and co-morbidities and the risk of lung metastasectomy or the patient's refusal to accept lung metastasectomy into consideration. The choice of RFA is then an individual decision, based on the patient's risk-benefit relation. Once the decision was made, the interventional radiologist informed the patient of the risks and the possible complications and benefits of the procedure.

Indications for CT-guided RFA of HCCPM with curative intent were ≤ 5 cm diameter in size; five or fewer in number; no definite suspicious lesion other than lung metastasis on imaging studies at the time of HCCPM diagnosis; a distance between the lesion and the pulmonary hilum vessel, main bronchus, or organ belonging to mediastinum of 1 cm or more with possibility of safely complete ablation (except for one patient with lesion distance of<1cm; no contraindications for RFA such as coagulopathy (prothrombin time greater than l.5s, platelet count less than $100x10^9$/L) and not previously received other treatment, such as chemotherapy and/or radiation therapy for HCCPM.
Pretreatment workup included a complete history, physical examination, and imaging modalities including lung, abdomen, and pelvic CT scans with contrast medium, brain MRI, and electrocardiogram, and laboratory examinations, including complete blood cell counts, blood chemistry, viral titers (such as hepatitis B virus, hepatitis C virus, and human immunodeficiency virus), and coagulation profile examinations.

RFA Procedure

Before the procedure, all the patients fasted for 12 hours. The RFA procedure was performed in a hospital CT room by two experienced interventional radiologists, a technician, an anesthetist, and a nurse. All procedures were performed under real-time CT-fluoroscopic guidance (CTi; GE Medical Systems, Milwaukee, Wis) with 5-mm collimation and 10-50 mA. The patient was placed in the appropriate position according to the location of the tumor with electrocardiograms, blood pressure, and saturation of blood oxygen monitored throughout the procedure. Intraprocedural pain was treated by using a combination of local anesthesia (subcutaneous 1% lidocaine) and conscious sedation (propofol, 1-2mg/kg/h), or general anesthesia (enflurane/isoflurane). General anesthesia (15 sessions, 15 patients) was administered when the tumor was close to the pleura or when the patient requested for it.
After thoracic CT scanning was performed, the precise location of the target lesion was identified and the puncture angles and depths of electrode insertion were thereby confirmed. Local anaesthesia (subcutaneous 1% lidocaine) was administrated at the selected puncture points, and then a 0.5-cm surgical incision (subcostal or intercostal) was made. Two grounding pads were placed on the proximal thighs. The RF electrode was carefully inserted into the center of the tumor at a predetermined angle in a stepwise manner under CT scan guidance.
A monopolar internally cooled electrode (Cool-tip; Valleylab, MA, USA) was used for all lung RFA procedures. The procedures were performed according to the manufacturer recommended protocol. Specifically, a 17-gauge single internally cooled electrode was applied for 12 minutes per ablation with one or two session for each site in the tumor using an impedance-controlled algorithm for the Cool-tip system. Each patient underwent 1~3 sessions of ablation and the tumors larger than 3 cm received multiple overlapping ablations to obtain the ablative margin. A maximum of 3 lung tumors were treated on the same side of the lung. The remaining tumors were treated by RFA on the following week to minimize the possible procedure-related complications, especially for pneumothorax. At the end of each ablation session, the electrode track was ablated to avoid possible bleeding and the risk of puncture-related implantation metastases. The technique successes and possible complications were evaluated by an additional CT scan immediately after

the procedure; and ablation was considered successful with the presence of ground-grass opacity diameter 0.5 to 1.0 cm in diameter greater than the lesion. Patients were discharged usually 1 to 3 days after the procedure.

Postablation evaluation and Follow-up

Postablation follow-up evaluations were performed at 1, 3, 6, 9 and 12 months; at 6-month intervals thereafter with clinical and radiological examinations. Local efficacy was assessed according to the modified RECIST criteria together with the level of serum AFP one month after the RFA procedure. A serum AFP response was defined as a value<20μg/L, or a2≥50% reduction.
The time to local tumor progression (TTP) was the interval from the completion of all treatments to the re-emergence of targeted lesions, or the detection of new metastatic lesions. The OS period (including the median survival time and 1-, 3-, and 5-year OS rates) for each patient was defined as the date of entry into the treatment to the date of the last visit before January 31, 2012 or death from any cause.

Statistical analysis

Survival outcome was calculated by Kaplan-Meier survival analysis. Prognostic factors for long-term survival were identified by univariate survival analysis, according to Cox proportional hazards regression methodology. Factors with a p-value of <0.05 in univariate analysis were included in multivariate analysis. Statistical significance with a p-value of less than 0.05 was considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences program (SPSS v16.0, SPSS Inc., Chicago, IL, USA).
In order to evaluate the local control of HCCPM and OS, univariate and multivariate analyses were performed using the time interval between diagnoses of the HCC and lung metastases, number of tumors, and size of the largest tumor, hepatic virus infection, ZPS, serum AFP level before initial lung RFA, the response after initial lung RFA. Multilevel analysis was used to adjust for the potential correlation of multiple tumors in a single patient. The hazard ratio (HR) and 95% confidence interval (CI) for each variable were estimated.

Results

No death was related to the RFA procedure. The major complication was symptomatic hemothorax (3.9%, 2/51) treated with drainage. Minor complications (19.6%, 10/51) included self-limited minor hemothorax, a low-grade fever (< 37.5°C), which were easily controlled and well tolerated.
A total of 51 RFA sessions (mean per patient: 1.76; range, 1-5) were successfully performed on 58 HCCPM lesions with CT guided RFA for 29 patients. One month after initial RFA procedure, complete ablation after initial lung RFA was achieved in 61.5% (13/29) of the patients. 18.8% of the patients with residual tumor revealed by enhanced CT scan and additional RFA were performed in all these 16 patients. Serum AFP level response rate was 80.6%.
The mean TTP was 15.6 months (range, 0-55 months. During follow up, 61.5% (13/29) of patients experienced only one recurrence of targeted lesions, 27.6% (8/29) experienced new non-targeted lung lesions progression and treated with additional lung RFA.
During the mean follow-up period of 62 months (range, 5 to 75), 38% (11/29) patients are still being followed up, while 62% (18/29) patients have died resulting from the progression of hepatic lesions. From the entry into the treatment for HCCPM, the median survival time after initial lung RFA was 18.9 months (range, 2 to 66). The 1-, 3-, and 5-year OS rates were 71.6%, 27.9%, and 9.3%, respectively. For the CR cases, the median survival time and OS were 21 months and 87.5%, 50.0%, and 25.0%, respectively, and for PR were 16 months and 62.5%, 11.7%, and 0%,

respectively. Prognostic factors of overall survival were analyzed and reported, serum AFP level before lung RFA (HR = 1.4, 95% CI 1.2-5.9; P = 0.028) and response to initial lung RFA (HR = 2.5, 95% CI 1.4-4.5; P = 0.002) were significant predictors for overall survival.

Discussion

Advances in surgical techniques and locoregional therapy for HCC have resulted in better surgical outcomes and long-term survival in recent years. However, the recurrence rate after curative resection of HCC is high, with distant metastasis most frequently found in the lung. Because local control of intrahepatic recurrence has been undertaken in a more proper and safe manner, there has been an increase in the number of deaths resulting from respiratory failure from pulmonary metastasis. Hence, active treatment for pulmonary metastasis from HCC has received landmark clinical attention. RFA is gaining increasing acceptance as a safe and effective therapeutic modality for primary and second lung tumors. In the present study the 5-year overall survival for HCCPM was 71.6 % with a mean survival after initial lung RFA of 18.9 months. The reported data revealed that the median overall survival after surgical metastasectomy for solitary lesion was 16-52 months and a median 5-year survival was 0-75%. Compared with these data, lung RFA in selected unresectable patients might provide a relevant survival benefit. Besides, the survival outcomes of the present study are comparable with previously published reports. Median overall survival in the literature for HCCPM patients ranges between 15 and 63 months and 5 year overall survival between 21 and 80%.

Our study has shown that lung RFA is a relatively safe and useful therapeutic option for selected patients with unresectable HCCPM. It showed the TTP of 15.6 months in overall cases which is similar to the figures of PFS in HCCPM with metastasectomy, however, median OS of 18.9 months in our report using RFA procedure is lower than that of pulmonary metastasectomy with a median OS of 29 (range, 16-52) months, median progress-free survival of 19 (range, 7-38) months and a median 5-year survival rate of 28% (range, 0-58%) in several studies. The results might be explained that the difference study population in terms of more lung metastatic lesions in bilateral lungs or being multiplies in our study in comparison with metastasectamy cases with solitary metastatic nodules. It is noteworthy that the subgroup of patients with CR after RFA showed a median survival rate (21 months, OS of 87.5%, 50.0%, and 25.0% at 1-,3-,5- years, respectively) that was similar to the figures of on pulmonary metastasectomy in recent studies. Given that all our patients were not surgical candidates, lung RFA seems to provide survival benefit.

The CR rates we obtained are also similar to the previous studies of lung metastasis tumors treated with RFA procedure, but it is significantly higher than that obtained on primary lung cancer with RFA procedure. The reason are: 1) More infiltrative tumor would be predicted to have a higher risk of tumor progression associated with the RFA procedure; since metastatic lesions are spherical in shape with a smooth margin which is easier to obtain cleaner regions with the RFA procedure. Closer follow-up surveillance of our patients, who had been enrolled into our clinical studies, facilitates early detection of HCCPM and prompt treatment. 2) Increasing concentration of serum AFP is associated with diagnosis of HCC in 70% of Asian patients. Correspondingly, serum AFP level is a sensitive marker to monitor the response assistant with follow-up.

In univariate and multivariate analyses, the maximum tumor diameter and number were not found to be significant prognostic factors. Serum AFP level before lung RFA and complete response to initial lung RFA were found as significant predictors for overall survival, while the number and size of the lung metastases were not prognosis for survival. That may be explained that HCCPM treated with RFA in our study was limited as no more than 5 and less than 5 cm in diameter, the CR rate and OS of the patients with 1, 2 lesions and lesions diameter less than 3 cm were similar with the reports of pulmonary metastasectomy with one site of extrahepatic lesion. The patients with more than 3 lesions were treated with more than one session of RFA to reduce the incidence of pneumothorax. Besides, patients with bilateral lung metastases are poor candidates for surgical intervention. In the present study, tumor distribution was not a prognostic factor, which suggests

an advantage of lung RFA over surgical intervention. The lesser invasiveness of the former appears to support the indication of lung RF ablation. In addition, RFA can also ablate with multiple lesions with synchronous or metachronous presentation of HCCPM patient to reach the relatively long OS, but, the contribution to prolong survival of metastasetomy has hindered for number of lesions, metachronous metastasis and undetected micrometastatic lesions present at the time of surgery. Prognostic factors identified in our study will help to stratify those patients who may benefit from lung RFA.

In our study the profile of procedure-related complications are infrequent and the most frequent complication was pneumothorax in ablating multi-metastatic lung lesions and the incidence was no more than those reported in previous studies to be associated with RFA in treating solitary tumors, which was mainly due to the minimum puncture numbers during the insertion of electrode into the target tumor under CT guidance by experienced interventional radiologists, as studies had shown that the number of insertions of the radiofrequency electrode was a significant risk factor causing pneumothorax. Besides, symptomatic pneumothorax can be controlled easily by using chest tube placement. Other complications such as haemorrhage, pneumonia, tumor seeding along the needle tract and subcutaneous emphysema were not observed in the present study.

As patients with unresectable liver cancer or who are not surgical candidates generally have significant comorbidities, together with low mortality and morbidity, repetitive application of RFA is a feasible treatment alternative, which is especially benefit for metastatic tumors with the nature of multiple origins.

There were some limitations which may affect clinical value of the study. Firstly, this was a retrospective study with a small sample size possibly resulting in insufficient statistical power. Besides, the diagnosis of HCCPM was mainly confirmed by the enhancement pattern observed on contrast-enhanced CT studies together with the level of AFP. Lastly, the use of two different probes for performing the RFA could have introduced some additional variability in the outcomes.

Conclusion

Our study showed the CT-guided RFA is a safe and effective treatment option with curative pursuits or prolong survival for unresectable HCCPM patients with well-controlled intrahepatic lesions. Further larger prospective studies or randomized controlled trials are needed to confirm the safety and efficacy of RFA for unresectable HCCPM.

Acknowledgements

The authors are grateful to Nicola Moscufo, PhD. (Brigham and Women Hospital, Harvard Medical School, Boston, USA) for editing the manuscript and Ying Guo, PhD. (Sun Yat-sen University Cancer Center, Guangzhou, China) for her expert guidance in data analysis.

Declaration of Interest

This work was supported by grants from the Ministry of Public Health of China, the national major projects in medical scientific and technological innovation (2008ZX09312-002). No conflict of interest exists among any of the authors. The authors alone are responsible for the content and writing of the paper.

Oncothermia Journal 10:91-98 (2014)

Oncothermia research at preclinical level

Andocs G[1], Okamoto Y[1], Balogh L[2], Meggyeshazi N[3], Szasz O[4]

(1) Department of Veterinary Clinical Medicine, School of Veterinary Science, Tottori University, Tottori, 4-101 Minami, Koyama-Cho., Tottori Pref., Japan

(2) Frederic Joliot Cure National Research Institute for Radiobiology and Radiohygiene, 1221-Budapest, Anna u. 5, Hungary

(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, 1085-Budapest, Ulloi ut 26., Hungary

(4) Biotechnics Department, Faculty of Engineering, St. Istvan University, 2100-Godollo, Pater K. u. 1., Hungary

Oncothermia research at preclinical level

Objectives of the work

Our paper has double objectives: first it is connected to the human medicine, aiming to model the natural human tumors much more realistically than the rodent tumor models. In this line we treat spontaneously occurring tumors and metastases on companion animals. During these experimental oncothermia treatments we can collect a huge amount of measured electromagnetic parameters that can help to understand what is really happening during oncothermia treatment and can help to optimize the next generation oncothermia devices. The other goal is to develop a dedicated tumor treating device for the veterinary market because it does not have a really effective, relatively cheap and easy to use method to fight against pet cancer. We show that oncothermia has definite benefit in both the objectives.

Introduction

Contrary to the human hyperthermia applications in oncology, the history of hyperthermia in veterinary medicine has only 50 years. The very first veterinarian oncology case was published in 1962. The tendency of the number of publication was rapidly growing till the 1980s and declined sharply in the next decades (see Figure 1.)

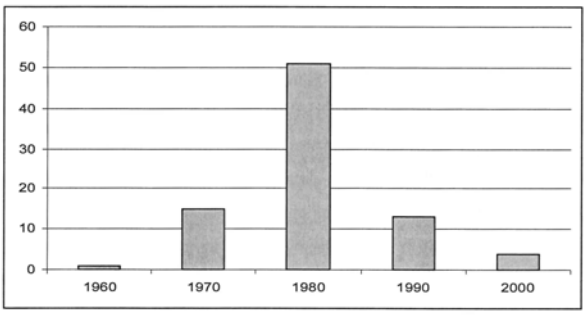


Figure 1. Number of publications on veterinary hyperthermia by decades

The first hyperthermia applications concentrated on the whole-body heating with various techniques. The systemic treatment was devoted to act in the advanced cases of distant metastases. The treatments were used alone or combined with local radiation on the primary tumor. Experiment of rodent tumor models in vivo concluded with unexpected results: the systemic (whole-body) hyperthermia does not able to destroy completely the primary tumor, but it also does not block the metastatic developments, oppositely it promotes the progression of the distant metastases. In veterinarian clinical trial of dogs having osteosarcomas without evidences of metastases, the local radiation combined complementary with whole body hyperthermia was studied. The result was surprisingly bad: the combined treatment was not effective on the primary tumor, but rapid and massive metastases were developed in far distant organs including the lung. This had blocked the research in this direction; the veterinarian application of the hyperthermia even in combined therapies was not plasticized in veterinary field.

Disadvantages of the whole-body hyperthermia had formulated the demand of the local (regional) heating combined with local radiation techniques. At first the ultrasound heating was studied, but its disappointing low efficacy had blocked these trials. The other promising trials were made by

infrared laser-heating, but its high expenses and the necessary complications by the invasive way, which was the consequence of the low penetration depth of the radiation; this method has limited spreading in veterinary clinical practices. After these disillusive trials, let us summarize the local (regional) heating methods by electromagnetic effects in veterinary applications.

The aim in the local (regional) heating in general was a selectively achieved high temperature (42-43°C) in the target, and the technical solution of the energy delivery was irrelevant. The invasive interstitial microwave treatment and all the other non-invasive solution were equally handled, the only point was the temperature in the target, irrespective which technique was applied. The so-called LCF (local current field) technique was especially dedicated for veterinarian applications, and it was applied as monotherapy in most of the cases. The device (named RF-22 Thermoprobe) was developed in the early 1970s, and its results were dominantly published in the early 1980s. This device was accumulator operated, handheld construction with 10 W maximal output power, using 2MHz frequency between two sheet electrodes having a distance of 5 mm in 12 cm length.
It was applied solely for small size (max. 5-10 mm diameter) surface-located tumors (mainly squamous cell carcinomas). To avoid the overheating a temperature sensor controlled the process, regulating less than 50°C. There were speculations (R.L. Grier) about a temperature as high as 59°C, because the supposed thermal conduction allows this gradient from critical 50°C measured on the electrode surface. The same author reports very good results in cases of surface-located tumors (malignant melanoma, squamous-carcinoma, fibrosarcoma, perianal adenoma, etc.) of small pets (dogs, cats): a single shot treatment with 30 second had positive response in 85% of the cases, 70% complete remission, 15% partial regression, and 15% had no benefit from the treatment.

Treatments having no benefit were in cases when the tumor was expanded deeper than 2 mm. This author has treated large animals (horse, cattle) with this LCF technique too. 50% of these tumors were resistive against other therapies like surgery, radiation or immunotherapy. The LCF treatments, made by max. 3 times and max. during 30 seconds, were successful: 80% had complete remission, while 16% was reacting partially. In conclusion cases of large tumors (larger than 5 cm) or deeply extended locations (deeper than 2-3 mm) the LCF method is not effective. Kainer treated eyelid squamous carcinomas of cattles, and reporting 91% complete remission in all the cases. The last reference which we found in the literature was published in 1990, showing the case of squamous carcinoma on the eye of a high-values sport horse. The LCF was successfully applied in combination with brachytherapy (Au^{198}). From this time we could not found any published data with this method, which anyway was applied successfully for small, surface located tumors.

Numerous methods were developed for deeper applications of RF-current. The simplest one, when the tumor selection is made by the needle insertion into the tumor volume. Such method was used in combination with radiation therapy for nasomaxillar fibro sarcomas dogs, which anyway has very bad prognosis (median survival time is 1 month). Numerous needles were inserted from the nose-surface of the dog according to the contour of the deep-seated tumor, oppositely in two rows. The needles were wired in one row, and the rows were supplied by 500 kHz RF generator. The temperature was measured by invasive sensors in the tumor, controlling the maximal temperature to 43 °C. This was reached by 5-15 W output power. The heating up period was 15 min, and there was a plateau keeping the tumor on 43 °C for 30 min. 2-4 treatments were applied in 72 h intervals in four treated animals. Complete remission was reached in case of three out of four. One was no successful. One had recidive in follow up, while two was completely free of disease. Dewhirst and collaborators had continued the practice of 500 kHz interstitial treatment, but mixed with the 2.4 GHz microwave application, taking care only on the temperature as parameter, keeping the 43°C as the "dose". Reviewing later, the authors remark the better observed effects in case of 500 kHz than 2.4 GHz applications. This needle invasive modality has a pure electric field version (ECT) too, which became increasingly popular.

Magnetic methods were applied also in veterinarian practice, and intensive research is made in this field nowadays. There are numerous problems arisen compared to the non-invasive heating methods: (a) the focusing is artificial, where the magnetic material is inserted, the energy absorption is concentrated, (b) the magnetic fluid spread by diffusion and blood-perfusion from the target, (c) the temperature can not be concentrated in a localized volume among the well conductive heat-exchanging conditions like the living state, (d) the method is invasive, having numerous problems of possible infection, bleeding, inflammation and cellular dissemination, (e) the inserted material has to be annulled at finishing the treatment procedures (f) it is too expensive and complicated for veterinary use.

The microwave radiation as a well oriented energy beam could be easily used for hyperthermia therapies. Radiotherapy was combined with sophisticated 433 MHz and 915 MHz hyperthermia systems; and only 51% of the cases were complete remission, and 35% was partially responding. No response was observed in 14%, despite of the combined therapies. Despite the theoretically easy focusing of microwaves, numerous practical problems occur: at large tumors to construct a unified temperature distribution was not possible, while in small tumors the focusing was problematic, burning the connective tissues as well.

Other microwave treatment was done by the ring-array focusing at 140 and 433 MHz frequencies. The temperature was measured invasively.

The 2.4 GHz microwave treatment combined with radiotherapy was successfully applied in cases of canine's hemangiopericitoma. The complete remission rate was 82% while the overall response rate was 91%. Important observation was made in spontaneous canine soft-tissue sarcomas by comparison of the various temperature levels. The measurements show certainly higher blood-perfusion rate in the tumors on lower temperatures than in higher ones, which has definite importance in the combined therapy with radiation.
Special microwave application was done for cats, increasing the intake of the 99mTc labeled liposomal radiofarmacons.
Treatments of the surface tumors were made by RF (13.56 MHz) treatment combined with the magnetic targeting (Magnetrode) in deeper regions. This study showed the improved tumor-selection effect of this frequency, but the method was not further-developed afterwards.

Oncothermia method (OTM) has been applied in human oncology since 1989. Its clinical results excellently show the advantages of the method, however, the details of its mechanism are being intensively investigated even now. Oncothermia research group conducts investigations at all levels of scientific research, from in vitro studies to human clinical trials. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven in vivo, but the complex electromagnetic parameters playing crucial role in achieving these antitumor effects have not yet exactly been determined. On the other hand, in the veterinary oncology practice there is a huge need for an effective treatment to cure malignant diseases due to the increasing incidences of cancer in pet animals, and the lack of a really effective and relatively cheap method to cure.

Materials and methods

Oncotherm created a specialized research device for preclinical investigations/veterinary clinical use, the VetEHY510 system. This Oncotherm-veterinarian device is developed to eliminate the previous problems and fulfill the demands above. The system is capacitive coupled and simple for use. Its schematics are shown below. The VetEHY510 system was created to serve dual purposes:
I. To give a powerful, effective and easy- to- use device for veterinary oncologists to fight against pet cancer and to provide information about the treatment efficacy of oncothermia method for comparative clinical oncology.

II. To Collect information and a wide range of measured electromagnetic parameters, which can help to optimize the treatment protocols and clarifying the real role of electromagnetic treatment parameters could provide the best clinical outcome.
Using the VetEHY device in Tottori University, Veterinary Medical Center, we treated companion animals (dogs and cats) having different kinds of tumors (liver tumor, soft tissue sarcomas, lung tumor, lymphomas, melanoma, etc.) under the supervision of professional vet oncology specialists and kept the animal ethical regulations.

The device works on the basis of RF-current flowing through the chosen part of the animal. This has various effects:
General heating by the absorbed energy of the current
Automatically focuses on the tumor-lesion
Selectively targets the malignant cells
Initializing special membrane associated effects (signal pathways), promote natural processes (apoptosis) to kill the cancerous cells.
Builds up again some cellular connections (adherent connections and junctions) blocking the dissemination of the malignant cells.
Vet-EHY treatment-device is designed for treating of oncology cases of companion animals (dogs, cats). It is a brand new development, with automatic tuning and many extra features for the veterinary applications and users' convenience.
It is built in a high-tech electronics based on the wide knowledge of the oncothermia applications in human oncology. The electrodes are flexible and widely consumable for various applications. It could fit for every body/forms and lesions.
Technical parameters
13.56 MHz output carrier frequency
0-80 W adjustable output power
LCD screen to display actual treatment parameters
Digital power and treatment time control
Microprocessor controlled, fast tuning
Latest developments of fractal fluctuation modulation
RS232 output for treatment data logging and full computer control of the device
Vet-EHY makes conductive heating. It is a modulated radiofrequency-current flowing through the targeted volume. The patient is a part of the electric circuit, fully and permanently controlled by the electronics and the treatment is carefully adjusted to optimal in-situ. The treated tissue is imperfect dielectric-material of the condenser of the circuit.
The method is self-selective, using the better conductivity of the extracellular electrolyte around the malignant cells due to their higher metabolic activity and lower pH.

The VETEHY device was designed to fit all the clinical demands in veterinary oncological practice:
The applied frequency is accurately 13.56 MHz (free frequency, no shielding is required, harmonized with the electromagnetic compatibility standards.)
The applied power limit is 80 W, which could be adjusted in 1W steps.
The tuning is fully automatic, (auto-matching).
The standing wave ratio is measured, the S11 attenuation is indicated on the display in dBm. (Approximately 20 dBm corresponds to SWRl.l, and the SWR decreases to 1.01, 1.001 ... by 30, 40, .. dBm, respectively. (The SWR roughly could be described as the sum of the forwarded and reflected power divided by their difference. Consequently, SWR=1 means the ideal situation when no reflected power is present, all the forwarded power is absorbed by the target.
The device has RS232 standard serial port to register the actual treatment, and all the parameters can be controlled by an external PC.
The electrode was designed to fit automatically into all the shapes and form of the animals body due to the significant anatomical differences of the different dog breeds.

The treatment time could be adjusted and shown by count-down in minutes (maximum 90 min). The treatment power is in Watts (W), (maximum 80 W).
The tuning in the beginning of the treatment is made by 3 W power. The increasing of the power is only possible, if the tuning is finished.
The treatment pad has the electrode holder and the counter electrode is a metallic sheet of the treatment table, or a forceps counterpart.

Results & discussion

The literature clearly shows the problems of the hyperthermia in veterinary practice. Until now such a device does not exist for veterinary use, which
Is effective enough for treatment,
Has universal, versatile applications
Could be applied as monotherapy in cases when no other possibilities are available
Is easy to use in veterinary practices
Is inexpensive, or its investment turns back quickly.
Scientists in oncology are just starting to realize the importance of the involvement of veterinarians in a real preclinical research work. The newest edition of Withrow and MacEwen's Small Animal Clinical Oncology briefly summarizes the aspects of companion animal cancer that enables attractive comparative models in a real preclinical investigation.

To emphasize the real value of the information which can be collected during the experimental treatment of companion animals, we would like to cite some points from the afore-mentioned book:
Companion dogs and cats are immunologically intact animals (like humans) as opposed to many experimental models of rodents and other animals.
Cancers seen in practice has spontaneously developed as opposed to experimentally induced, and they recapitulate the natural human and veterinary condition better.
Companion species have a higher incidence of some cancers (e.g., osteosarcoma, non-Hodgkin's lymphoma) than humans.
Most animal cancers progress by more rapid rate than their human counterpart. This permits more rapid and less costly outcome determinations such as time until the metastasis, local recurrence, and time of survival.
As fewer established "gold standard" treatments exist in veterinary medicine compared to human medicine, it is ethically acceptable to attempt new forms of therapy (especially single-agent trials) on an untreated cancer rather than to wait to initiate new treatments until all "known" treatments have failed, as it is common in the human condition.

1. Companion species' cancers are more akin to human cancers than are rodent tumors in terms of patient size and cell kinetics. Dogs and cats also share similar characteristics of physiology and metabolism for most organ systems and drugs. Such correspondence allows better and safer comparison of treatment modalities such as surgery, radiation, and chemotherapy to be made between animals and humans.
2. Dogs and cats have intact immune systems as opposed to many rodent model systems, which allows immunologic assays and treatment approaches to be explored.
3. Companion animal trials are generally more economical to perform than human trials.
4. Companion animals live long enough to determine the potential late effects of treatment.
5. Dogs and cats are large enough for high-resolution imaging studies and multiple sampling opportunities, as well as for surgical intervention.
These spontaneously occurring tumors are the best "models" of human malignant diseases. Getting treatment information and experiences on the behavior of these tumors from these pet patients are extremely valuable. These info can be directly transformed to human practice to improve the clinical results. (Figure 2.)

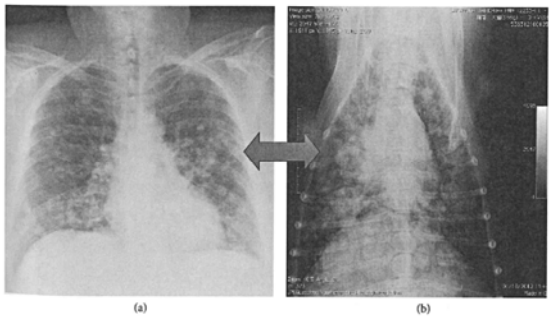


Figure 2. A representative example of the similarity of the clinical manifestation between humans and companion animals. A: X-ray image of the pulmonary metastases from recurrent melanoma in a human patient (image courtesy of Dr. D.G. Borgeson), B: X-ray image of the pulmonary metastases from melanoma in a labrador dog (patient from our veterinary hospital)

Shrinkage of tumor size, decrease of the tumor-associated pain and improvement of the quality of life of the animals were observed after oncothermia monotherapy treatments. More emphasized beneficial effects were observed, when oncothermia was used in combination with low dose chemotherapy. Veterinary oncothermia clinical investigations are still in progress. To illustrate the clinical success in relatively severe cases, some case reports are presented:

Case 1 Case No.:12082, 8 years old mini dax. Symptoms: severe ataxia, the dog was not able to move and keep his balance. Diagnosis: supposed meningioma in the cervical region (C3) as revealed by MRI investigations. Treatment: oncothermia treatment as a monotherapy (1 session-6 times in 2 weeks, after oncothermia treatment 1-2 times/month) using the special forceps electrode. (Figure 3.)

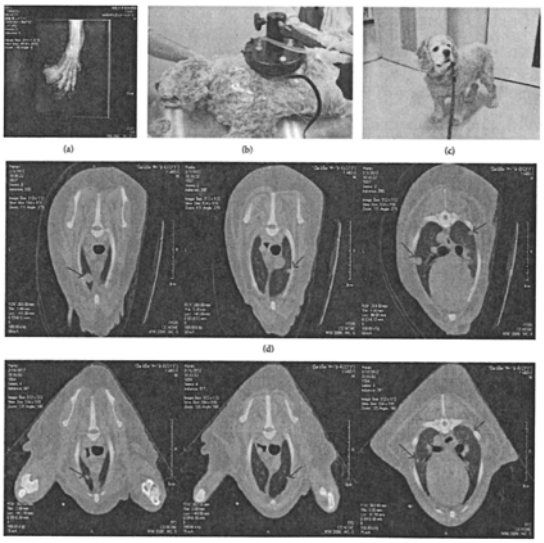


Figure 3. S*ummary of case No. 1. A: at the time of the hospitalization the dog was suffering from severe ataxia and hemiparesis before the treatment, B: the dog during the oncothermia treatment, using a special forceps electrode, C: after several treatments the dog could walk and run again without any problem, D: before the treatment the MRI image showed a lesion in the cervical region (c3) which compressed the spinal cord causing the severe symptoms, E: after the first treatment session, the size of the lesion was decreased as shown in this MRI image, and the spinal cord was released from the pressure*

Case 2 Case No.:11461, a 8 years old castrated male Cocker spaniel. Diagnosis: melanoma was found on the toe of the right hind leg, which was surgically removed. Then severe lung metastases were developed. Treatment: low dose Carboplatine (2 times, 100mg/m2, what is 1/3 of the prescribed dose) + Oncothermia treatment (10 times in 2-3 days interval). Summary of case No.2.

A: X-ray image of the primary melanoma on the toe of the right hind leg, B: the dog during oncothermia treatment, C: the dog is still alive and has a good condition, without symptoms. D: CT image series in different slices of the lung before the treatment. Several large lesions can be visible in the lung, marked with red arrow, E: CT image series of the same slices of the lung after the treatment. The size of the lesions are dramatically decreased and in some cases completely disappeared

Case 3 Case No.:9417, 9 years old, castrated male golden retriever. Diagnosis: lymphoma in the thoracal cavity. Treatment: low dose COP (Cyclophosphamide-Oncovin-Prednisolon coctail, 2 times, 1/3rd of the prescribed dose) + Oncothermia (15 times at the first session then 1-2 times/month). The case is shown in Figure 3.

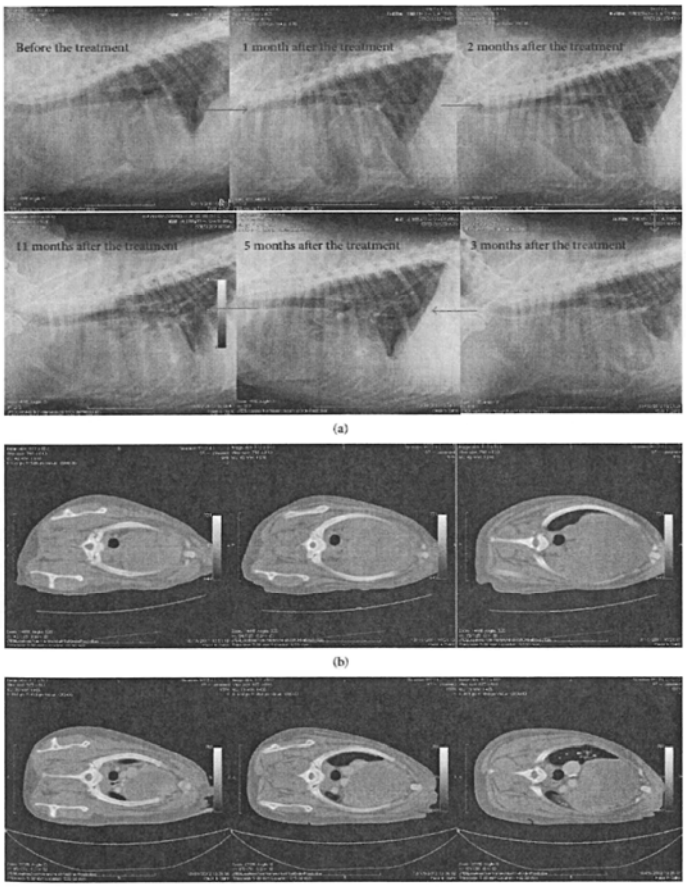


Figure 3. Summary of case No.3. A: In this X-ray image series the changes of the status of the lesion in the thoracal cavity can be tracked. B: CT image series in different slices of the lung before the treatment. The large tumor mass can be visible in the mediastinum, compressing the large part of the lung making serious difficulties in breathing. C: CT image series of the same slices of the lung 11 months after the treatment started. The size of the lesion significantly decreased, the lung was partially released from the compression

This case was a typical example of a rapidly progressing deadly disease becoming a manageable chronic disease.

During these treatments we measured and collected many valuable electromagnetic parameters which can help to understand what is really happening during oncothermia treatment in electromagnetic sense. Our opinion is that the accurate analysis of these precisely measured treatment-related electromagnetic parameters can help to reveal the most critical electromagnetic parameter to achieve the best biological response. Using the results of these measurements, we can

optimize the technical solutions of further developments of the oncothermia devices for the human oncological applications and for the veterinary practice, too.

Conclusions

Oncothermia method and the VetEHY510 system is a new hope to effectively cure companion animal cancer patients, fulfilling the huge demand from veterinary market. The newly developed VetEHY510 device is a powerful research tool for comparative clinical oncology and to understand the role of critical electromagnetic parameters to improve the oncothermia method in human clinical practice too.

Acknowledgement

Authors are grateful for the financial support of the present work by Oncotherm (Hungary/Germany) and by Tateyama Kagaku (Japan).

Clinical observation of Drug slow release depot therapy (DRSDT) in the treatment of 288 cases diagnosed with primary liver cancer

Jing-Peng[1], Ma Zhenlu[1], Guan Changjiang[1], Gaofeng[1], Yu Baofa[1]
(1) Baofa Cancer Hospital, Beijing, China

Objective
To explore the curative effect of Drug slow release depot therapy (DRSDT) for treatment of liver cancer.

Methods
To conduct DRSDT on 288 cases of liver cancer patients.

Results
According to WHO evaluation standard of curative effect for solid tumor, follow up and record the evaluation result, CE 5 cases, PR 151 cases, NC 125 cases, the total efficiency is 54,17% 3 year survival rate of stage II patients is 100%. And 1 year survival rate for stage III patients is 60.4%. After the treatment, the general condition of the patients improved, symptoms relieved, life quality improved, without serious complications.

Conclusion
DRSDT has better responses with less complications on different stages of primary liver cancer.

Keywords
Liver Cancer; Drug slow release depot therapy (DRSDT); curative effect

Oncothermia Journal 10:101-104 (2014)

Oncothermia in laboratory

Dr. Nora Meggyeshazi[1], Dr. Tibor Krenacs[1], Dr. Gabor Andocs[2], Dr. Oliver Szasz[3]

(1) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan

(3) Department of Biotechnics, Faculty of Engineering, St. István University, Budapest, Hungary

Oncothermia in laboratory

Theoretical background: The hallmarks of cell death

When is the cell dying? (=point-of-no-return)

- Massive caspase activation
- Mitochondrial transmembrane potential decreases (mitochondrial membrane permebilization)
- PS appears in the outer membrane of the cytoplasm.

When is the cell dead?

- The integrity of plasma membrane is lost
- The cells is fragmented
- The surrounding cells phagocyting the dead ones.

- Kroemer, G., et al., Classification of cell death: recommendations of the Nomenclature Committee on Cell Death. Cell Death Differ, 2005. 12 Suppl 2: p. 1463-7.
- Kroemer, G., et al., Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. Cell Death Differ, 2009. 16(1): p. 3-11.

How many ways to die?

A LOT…

… Extrinsic apoptosis, Caspase dependent intrinsic apoptosis, Caspase independent intrinsic apoptosis, Necroptosis (regulated necrosis), Autophagic cell death, Mitotic cathastrophe, Netosis, Parthantos, Pyroptosis Entosis

- Kroemer, G., et al., Classification of cell death: recommendations of the Nomenclature Committee on Cell Death Differ, 2005. 12 Suppl 2: p. 1463-7.

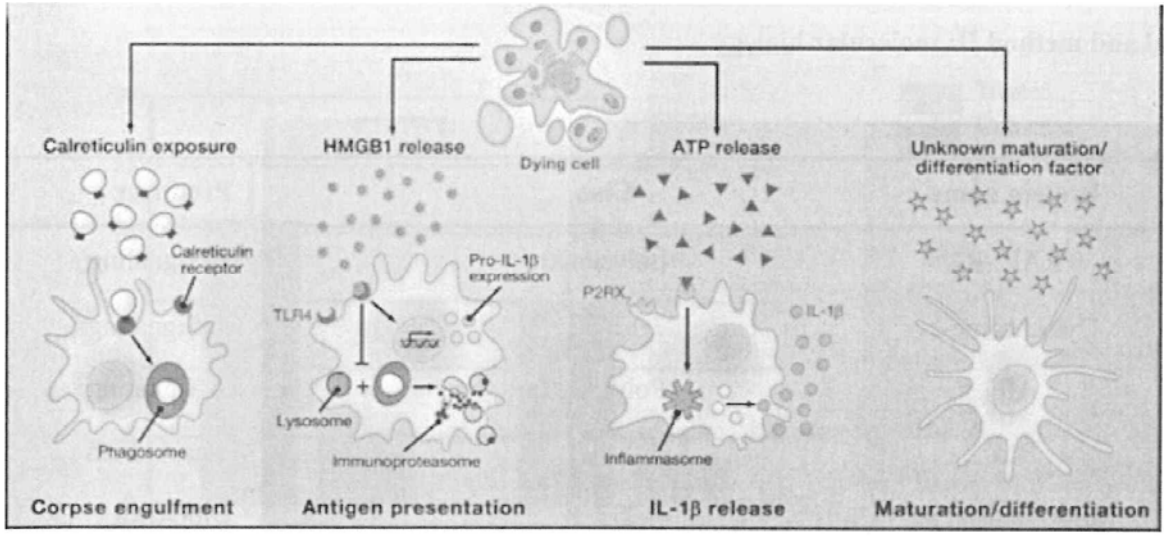
BUT

What can happen after the cell death? (possible interacions with the immune system)

- Inflammation can occure after accidental necrosis (professional phagocytes are involved)
- No immune reaction (usually in physiological apoptosis)
- Immunogenic cell death can occur after specific apoptosis inducers (photodynamic therapy, chemotherapy)

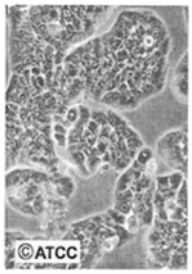
- Calreticulin exposure
- Membrane appearance of hsp70
- ATP release
- HMGB1 release

} Temporospatial pattern on the tumor cells in ICD

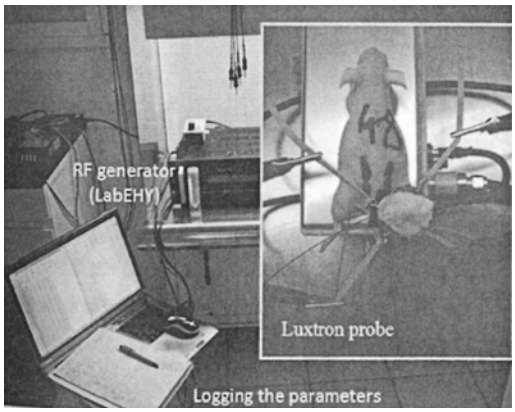


Kroemer et al. Journal of Experimental Medicine (2005 Dec 19;202(12):1691-701)

Material and method I: the model and treatment



BALB/c (nu/nu) mice inoculated with HT29 (human colorectal adenocarcinoma) in both femoral region (3*106 cells/0,1 ml) of 6-8 week old females



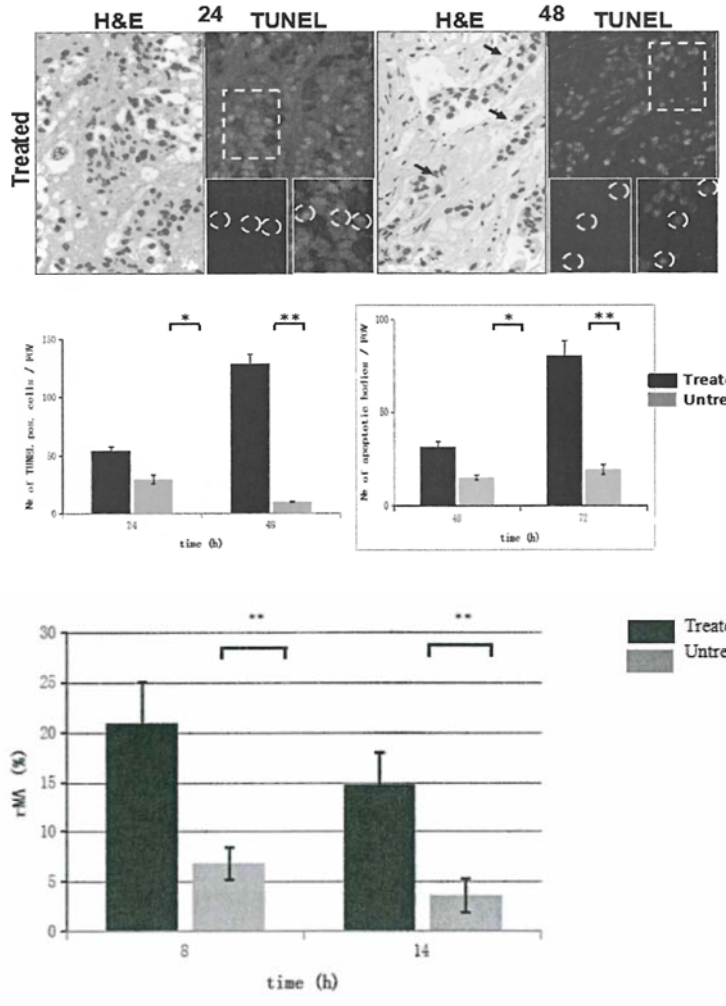
18 days later single shot treatment for (30 min), temperature between 41-42 ^{o}C. Sampling was carried out: 0, 1,4,8,14,24,48,72,120,168, 216h post-treatment

18 days later 30 min single shot treatment (treated tumor core temperature: 41-42 ^{o}C)

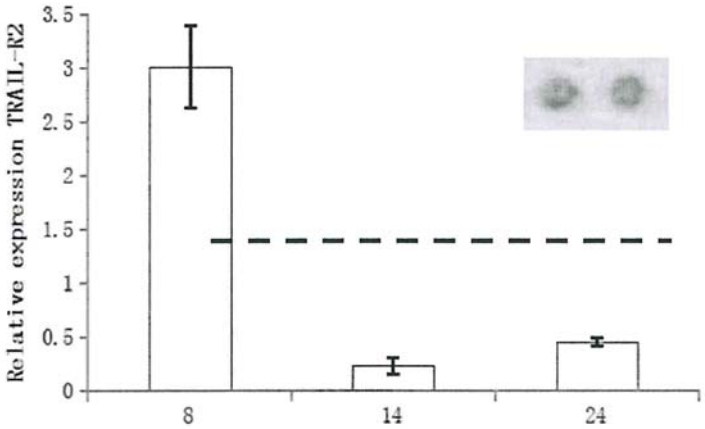
Material and method II: molecular biology

Protein name	Clon	Producer
TRAIL-R2	polyclonal	Cell Signaling
Cytochrome-c	136F3	Cell Signaling
AIF	Polyclonal	Cell Signaling
Bax	Polyclonal	Sigma Aldrich
Mitochondrial ag	113-1	BioGenex
hsp70	polyclonal	Cell Signaling
hsp90	Polyclonal	Cell Signaling
hsp60	Polyclonal	Cell Signaling
HMGB1	Polyclonal	Cell Signaling
CRT	Polyclonal	Cell Signaling

Results: Apoptotic bodies and DNA fragmentation

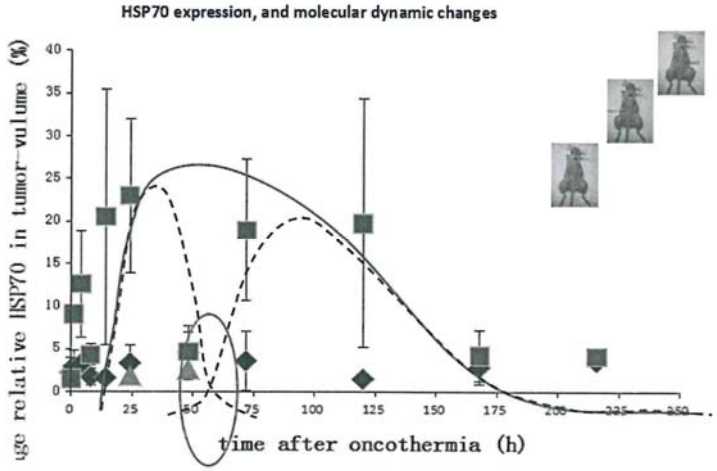


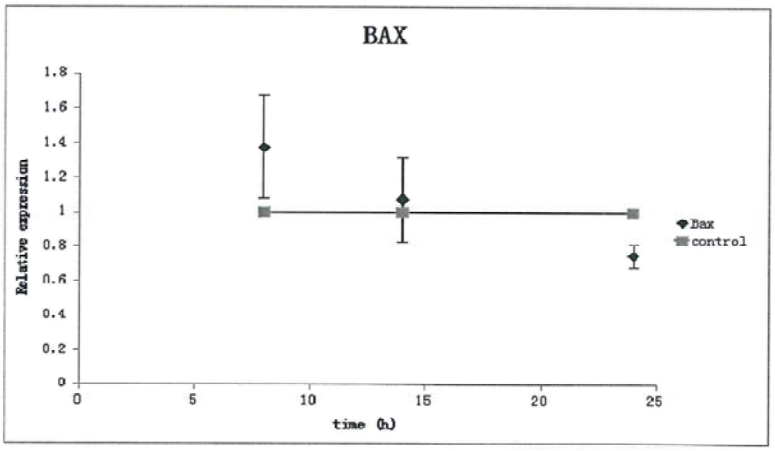
Untreated



Are there signs of immunogenic cell death?
Hallmarks of ICD: CRT
Hallmarks of ICD: membrane hsp70

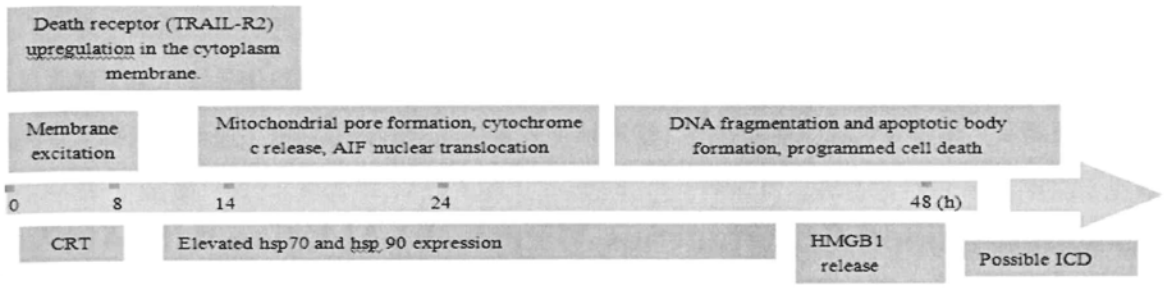
Heat shock protein 70 (HSP70)





Hallmarks of ICD: HMGB1 release

Summary



Oncothermia causes programmed cell death (as an obligatory event in ICD) with concomittant TRAIL-R2, calreticulin, heat shock protein upregulation and HMGB1 release from the nuclei.

Oncothermia Journal 10:105-105 (2014)

Ultrasound-guided Percutaneous Microwave Ablation with Artificial Pleural Effusion for Liver Tumors in the Hepatic Dome

Xiaoling Yu[1], Ping Liang[1], Dezhi Zhang[1], Zhigang Cheng[1], Zhiyu Han[1], Jie Yu[1], Fangyi Liu[1]

(1) Department of International Ultrasound, Chinese PLA General Hospital

Objectives

To evaluate the feasibility, safety, and efficiency of percutaneous microwave ablation (MWA) with artificial pleural effusion for liver tumors located in the hepatic dome.

Methods

112 sessions of artificial pleural effusion performed on 102 liver tumor patients were summarized and analyzed in our hospital. Among them, 31 hepatocellular carcinoma (HCC) patients treated by percutaneous MWA were selected as artificial pleural effusion group. The control group without artificial pleural effusion was matched with tumor size, tumor location and the histological grades of differentiation. The primary effectiveness rate, local tumor progression rate and tumor-free survival rate were compared.

Results

Artificial pleural effusion was achieved successfully in 110 of 112 sessions (98.2%), which helped to improve the visibility in 98.8% (82/83) and acquire safe puncture path in 96.3% (26/27). There were no statistic different between artificial pleural effusion group and control group in the primary technique effectiveness rate (p=1.000), the 1-, 2-, and 3-year local tumor progression rates (p=0.669), and the 1-, 2-, and 3-year tumor-free survival rates (p=0.979).

Conclusions

Percutaneous microwave ablation (MWA) with artificial pleural effusion could be a feasible, safe, and effective technique for liver tumors located in the hepatic dome.

Oncothermia Journal 10:107-108 (2014)

Influence of hyperthermia up-regulated CJIC on tumor invasiveness and its mechanism

Qin Li-juan[1]

(1) College of Basic Medical Sciences, Hebei United University, Tangshan 063000, China

Influece of hyperthermia up-regulated CJIC on tumor invasiveness and its mechanism

Aim

To explore the effect of junctional intercellular communication (GJIC) in hyperthermia-induced tumor invasiveness decreases process.

Methods

Dynamic monitoring of HSP70 and Cx43 protein expression of C6 cells (western blotting and immunohistochemical methods); Study of GJIC on glioma by scrape-loading dye transfer method, detection of the glioma invasiveness with crystal violet staining method.

Results

After the application of hyperthermia on C6 cells, the protein expression of HSP70 and Cx43 were gradually increased and then reached the peak at 30min and 120min respectively. The function of GJIC was positively correlated with the Cx43 protein expression in C6 cells. The glioma invasiveness is lower; the GJIC function is stronger.

Conclusion

Hyperthermia decreased glioma invasiveness is due to up-regulated the function of GJIC which could cause the tumor invasiveness attenuate by increasing HSP70 and Cx43 protein expression of glioma.

Keywords

Hyperthermia; Glioma; tumor invasiveness; Gap junctional intercellular communication; Heat shock protein 70; connexin 43

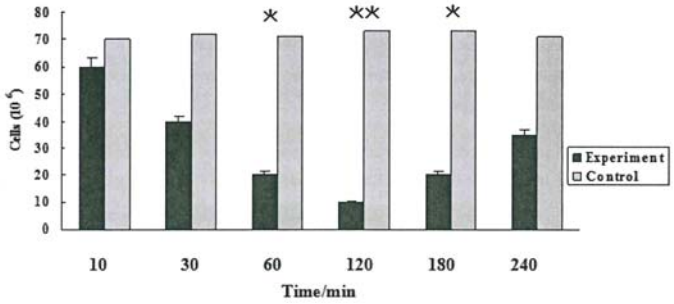


*Figure 1. Attached cells on the membrane downside after heat treatment (n=15). *P<0.05 and **P<0.01 compared with control group*

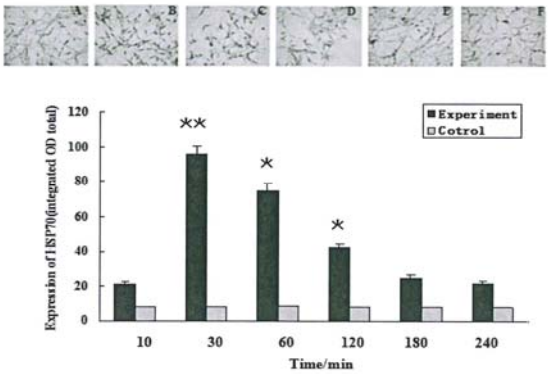


*Figure 2. Expression of hsp70 in C6 cells after hyperthermia (HT) (n=15). Anodic for HSP70 protein in experimental group and comparison group by immunohistochemical and underneath was propotional column diagram. A: hyperthermia 10 min; B: hyperthermia 30 min; C: hyperthermia 60 min; D: hyperthermia 120 min; E: hyperthermia 180 min; F: hyperthermia 240 min. *P<0.05 and **P<0.01 compared with control group*

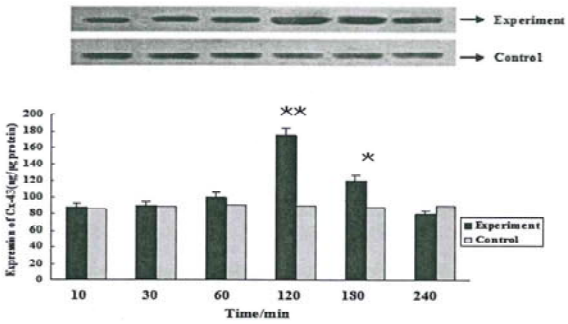


*Figure 3. Expression of Cx43 in C6 cells after hyperthermia (HT) (n=15). Anodic for Cx43 protein in experimental group and comparison group by western blotting and underneath was propotional column diagram. *P<0.05 and **P<0.01 compared with control group*

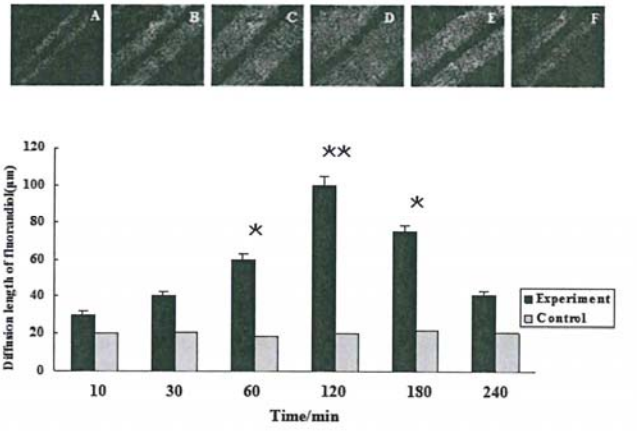


*Figure 4. Study of GJIC on glioma by scrape-loading dye transfer method (n=15). Anodic for diffusion length of fluorandiol in gliomas and underneath was propotional column diagram. A: hyperthermia 10 min; B: hyperthermia 30 min; C: hyperthermia 60 min; D: hyperthermia 120 min; E: hyperthermia 180 min; F: hyperthermia 240 min. *P<0.05 and **P<0.01 compared with control group*

Oncothermia Journal 10:109-109 (2014)

The Application of Hyperthermia and Hot Spring Rejuvenation

Sun Xiaosheng, Vice-President, Researcher[1]
(1) Guangzhou University of Traditional Chinese Medicine, Guangzhou, China

Abstract

This paper gives a review on the indications, impact factors, contraindications, and research development of oncological hyperthermia. It also gives an introduction to the development, mechanism and method of the hyperthermia application in hot spring life cultivation. In addition, this paper also concludes that hot spring reaches the goal of life cultivation through a combination of physical effects (temperature, buoyancy, pressure) and chemical effects (microelements). It is also proposed that hot spring life cultivation should work in accordance with the time, local and individual conditions.

Keywords

Hyperthermia, Hot Spring, Life Cultivation

Oncothermia Journal 10:110-110 (2014)

The Application of Large Dose of Moxibustion Therapy on Chronic Lung Disease

Qin Guanghui[1]

(1) The 1st Hospital of Traditional Chinese Medicine of Changde, Human 415000

Abstract

This paper presents a program on moxa-stick moxibustion therapy in large dose, which has a good effect in treating chronic lung disease.

Keywords

Chronic lung disease, Moxa-stick moxibustion therapy in large dose, 6 holes moxibustion box therapy, Program

TACE Combined with HIFU for Primary Hepatic Carcinomas: A Systematic review and Meta-Analysis

Li Zheng[1,2], Mi Deng-hai[1,2,3], Yang Ke-hu[1,2], Cao Nong[2], Tian Jin-hui[1], Liu Ya-li[1]

(1) Evidence Based Medicine Center of Lanzhou University, Gansu Lanzhou 730000, China
(2) The First Hospital of Lanzhou University, Gansu Lanzhou 730000, China
(3) The Second People's Hospital of Gansu Providence, Gansu Lanzhou 730000, China

Objective

To evaluate the clinical efficacy and safety of transcatheter arterial chemoembolization (TACE) combined with High-intensity Focused Ultrasound (HIFU) for primary hepatic carcinomas (PHC), and to provide the reference for clinical practice and research.

Methods

We searched foreign databases as Cochrane Library, PubMed, EMBASE, Web of Science and Chinese ones as CBM, CNKI, VIP and Wanfang with computer and also retrieved other sources as supplying, such as tracing related references. All relevant randomized controlled trials (RCTs) were collected to compare combination therapy and TACE alone. After literature screening, data extraction and quality evaluation independently conducted by two authors according to the protocal, the meta-analyses were performed using the RevMan 5.1 software.

Results

15 RCTs were involved with 1103 patients included. Meta-analysis showed: The 0.5-1-2-3-5 -year overall survival rate and total effective rate in the combination therapy group were superior to TACE alone, and there were significant difference ($P < 0.05$); 0.5-year[HR=5.12,95%CI=(3.46,7 .58)], 1-year [HR=3.03,95%CI=(2.26,4.06)], 2-year[HR=3.51,95%CI=(2.45,5.02)], 3-year [HR=3.60,95%CI=(2.42,5.37)], 5-year [HR=4.70,95%CI=(2.41,9.17)]. The incidences of combination therapy were lower than those of TACE alone on the indicators of Leukocytopenia, Nausea and Vomiting, Hepatic lesion, but there was statistically significant only on the indicators of Nausea and Vomiting. The incidences of fever was higher in the combination therapy group than the TACE alone group, and there were significant difference ($P<0.05$).

Conclusion

Compared with the TACE alone, TACE combined with HIFU can improve long-term survival rate and short-term curative effect, and it's feasible. But its long-term survival rate and security still needs to be further verified by more large sample and high quality RCTs.

Keywords

Liver Neoplasms, High-intensity Focused Ultrasound, Transcatheter arterial chemoembolization, Systematic review, Meta-Analysis, Randomized controlled trial

Oncothermia Journal 10:112-112 (2014)

Management of Complications from infrared whole body hyperthermia

Lu Yimin[1]

(1) Hyperthermia Centre, Clifford Hospital, Guangzhou 511495, China

Purpose

To discuss the prevention and treatment of common complications of tumor infrared WBH under medium or deep sedation.

Method

Retrospective analyzed the treatment and prevention measures of complications during the WBH around hyperthermia treatment and after the hyperthermia for the 108 cases of patients with tumor.

Effect

Through reasonable preventive treatments, no occurrence of serious complications on circulation, respiration, nervous system related to hyperthermia and around hyperthermia treatment and tardive empyrosis caused by thermal injury was observed.

Conclusion

For the common complications of tumor infrared WBH, by carrying out reasonable pre-treatments, it can control the occurrence of serious complications around hyperthermia treatment, reduce the occurrence of tardive empyrosis caused by thermal injury and improve the safety of WBH to tumors.

Keywords

Tumor, WBH, complications

Oncothermia Journal 10:113-113 (2014)

Traditional Chinese Hyperthermia - Moxibustion

Zhang Zili[1], Feng Jiayign[1], Cui Meina[1]
(1) Acupuncture Dept., Clifford Hospital, Guangzhou 511495, China

Abstract

Moxibustion is one of the external therapeutic methods in traditional Chinese medicine thermotherapy, and it plays an important role in dredging the channel, strengthening body resistance and eliminating evil, warming yang and correcting weakness, promoting qi to activate blood, and regulating yin and yang. The operation is simple, economic, safe and effective, and it has no toxic side effects and is easily accepted by patients, so it can give full play to its unique advantages in the prevention and treatment of diseases and health care. As one of the green comprehensive therapies, the moxibustion has been widely used in different clinical departments. Moxibustion has a characteristic of benign "two-way adjustment" effect on the overall function, and it has its own unique advantages in improving the general status of the patient and mobilizing the body's immune ability, etc.

Keywords

Traditional Chinese medical thermotherapy, Moxibustion, Mechanism

Oncothermia Journal 10:114-114 (2014)

Evaluation the effect of local hyperthermia on late stage lung cancer patients

Zhao Changlin[1]
(1) Oncology Department, Clifford Hospital, Guangzhou, China

Objectives
To investigate the treatment efficacy of local hyperthermia in advanced lung cancer.

Methods
75 stage IIIb and IV lung cancer patients who were not a candidate for surgery, radiotherapy and chemotherapy were given local hyperthermia (mainly non-invasive radiofrequency and endogenous field hypothermia). 20 times for each course, 1 hour for per time, once every other day. Treatment efficacy, survival rate and life of quality were assessed before the treatment, after the treatment and every 6 months.

Results
When in comparison with the control group, the treatment showed superior remission rate as well as statistically significant survival rate. In addition, the treatment group showed statistically significant quality of life including physical functions, emotions, general conditions, pain, shortness of breath, loss of appetite, cough, hemoptysis and chest pain.

Conclusions
Local hyperthermia can extend advanced lung cancer patients' survival and improve their quality of life.

Keywords
Lung Cancer; Local Hyperthermia; Quality of Life; Efficacy Assessment

Oncothermia Journal 10:116-117 (2014)

Results of oncothermia combined with operation, chemotherapy and radiation therapy for primary, recurrent and metastatic sarcoma

Tae Sig Jeung, Sun Young Ma, Jeasang Yu, Sangwook Lim

Department of Radiation Oncology, Kosin University College of Medicine, Busan 602-702, Korea

Correspondence: Tae Sig Jeung, M.D., Ph.D.: Department of Radiation Oncology, Kosin University College of Medicine, 34 Amnam-dong, Seo-gu, Busan 602-702, Korea

Results of oncothermia combined with operation, chemotherapy and radiation therapy for primary, recurrent and metastatic sarcoma

Porpose

Sarcoma is a rare type of cancer. Surgery is known as the only treatment that shows definite response. But it represents high incidence of local recurrence and distant metastasis. Although it shows partial response to chemotherapy, there is no definitive chemotherapy regimen to control it effectively up to now. It is also known that sarcoma is resistant to radiotherapy due to having large portion of hypoxic cells. Hyperthermia treatment can apply heat to hypoxic cell because hypoxic cell is weak at heat but it develops heat tolerance due to appearance of heat shock protein during treatment and treatment efficacy goes down as hyperthermia repeats. We have studied if oncothermia treats sarcoma effectively without developing heat tolerance.

Methods and materials

In Kosin University Gospel Hospital, we treated 13 sarcoma patients from Nov 2011 to Aug 2013 and analyzed the results. Patients aged between 18~73 years old. 6 males and 7 females. Histologic type is 2 rhabdomyosarcoma, 2 synovial sarcoma, 2 chondrosarcoma, 1 osteosarcoma, 3 leiomyosarcoma, 1 malignant peripheral nerve sheath tumor, 1 spindle sell sarcoma and 1 malignant fibrous histiocytoma (MFH). Treatment modality was 5 postoperative radiation therapy (RT) and oncothermia, 2 combined RT and oncothermia for primary lesion, 2 combined RT and oncothermia for recurrent sarcoma at original region and 4 combined RT and oncothermia for metastatic lesion. Oncothermia was applied 2~3 times a week. Post-operative RT was applied 50.4 Gy in 28 fractions and other RT was applied 30~39 Gy in 10~13 fractions. The combined chemotherapy with oncothermia for 1 case was applied to metastatic lung lesion.

Results and discussion

5 patients who received post-operative RT and oncothermia didn't show local recurrence. The metastatic lesion in lung was appeared in 1 case and received chemotherapy, RT 50.4 Gy and 12 times of oncothermia and the metastatic lesion in lung almost completely regressed (CR). 1 (MFH) out of 2 patients for primary malignant lesion in pelvis received RT 50.4 Gy and 27 times of oncothermia and showed almost CR grossly at CT scan. However this patient revealed local regrowing mass in 6 months from stopping oncothermia. The other one (peripheral nerve sheath tumor) for primary lesion received RT 30 Gy in 2 weeks and 108 times of oncothermia for 11 months and tumor mass at buttock regressed continuously as repeat oncothermia. This patient is still getting oncothermia. 1 out of 2 recurrence rhabodomyosarcoma patients received RT 30 Gy in 2 weeks and 12 times of oncothermia in neck for 1 month. Tumor was regressed partially.

But metastatic lesion was developed in retroorbital region. RT 30 Gy in 10 fractions and 12 times of oncothermia for 1 month was given and metastatic mass of retroorbital area also was shown partial regression. The other patient (chondrosarcoma) had recurrence at pelvic bone replacement region after surgery. This patient received RT 30 Gy in 2 weeks and 50 times of oncothermia for 8 months and showed partial regression. It was thought to be difficult to apply oncothermia due to metallic pelvic bone replacement but she strongly requested receiving oncothermia. There were no side effects caused by metallic bone when oncothermia was applied. In 6 months follow-up tumor size was not increased in CT images from stopping oncothermia. For 4 patients the metastatic lesions were treated. 1 patient received RT 30 Gy in 2 weeks and 48 times of oncothermia for 7 months in metastatic lung lesion and showed grossly partial regression. After stopping the

treatment, tumor mass was aggravated in size in 3 months, and 24 times of Oncothermia was applied again and it was partially regressed.
But after stopping treatment again, tumor regrew in 3 months and the patient received 11 oncothermia and tumor regressed but oncothermia was stopped due to patient's personal reason including economy. Other 1 patient (chondrosarcoma) had metastasis to chest wall and received RT 30 Gy in 10 fractions for 2 weeks and 47 times of concothermia for 4.5 months and showed partial regression. It was stable for 4 months. One patient had cervical spine metastasis (spindle cell sarcoma) from right buttock and received RT 30 Gy in 2 weeks and 5 times of oncothermia. We found that oncothermia effectively control pain and make metastatic lesion stable. 1 patient (osteosarcoma) had multiple lung metastasis and received chemotherapy and 84 times of oncothermia for 12 months. Metastatic cancer almost disappeared but one lesion that was out of the range of 30 cm diameter electrode progressed. So the patient received radiotherapy (48 Gy in 4 fractions, SBRT) for the progressed lesion. Side effect of chemotherapy was not serious as much as we expected when concothermia was combined with chemotherapy.

Conclusion

Primary, recurrent, and metastatic sarcomas were responded to oncothermia treatment and the mass regressed. When oncothermia was applied for long term, tumor mass was regressed slowly for oncothermia. It needs to study further more to see that complete regression can be achieved with oncothermia only and to increase effects with the combined modalities of oncohermia with chemotherapy and/or radiation therapy.

The 32nd Annual Conference of the International Clinical Hyperthermia Society (ICHS)

ICHS Papers

Oncothermia Journal 10:119-119 (2014)

The use of fever-range whole-body hyperthermia (FRWBH) in oncology in relationship to the therapeutic contexte

Stefan Heckel-Reusser, CEO[1]

(1) Heckel Medizintechnik GmbH, Blumenstrasse 18D – 73128 Esslingen, heckel@heckel-medizintechnik.de, Mobile: +49-711-6284799

Fever-range whole-body hyperthermia (FRWBH) with an elevation of body temperature to 38.5-40.5°C is widely used in complementary oncology in Germany. Most of the clinics consider it as an important basic module of an integrative cancer therapy.
But there are still a lot of questions on the mechanisms of FRWBH that are highly dependant from the therapeutic contexte.

Commonly accepted is the immune-stimulating effect of FRWBH especially for the recovery of the immune system after immune-suppressive cytotoxic therapies. This general immune-stimulating effect might also be crucial if FRWBH is used for lowering the risk of recurrence after successful primary therapy.

The mechanisms of FRWBH in the treatment of progressed and metastatic cancer disease are obviously more complicated. A direct anti-tumor immune effect seems to need a combination either with cytotoxic therapies, probably to enhance the antigen presentation to the stimulated immune system, or with cellular immunotherapies.

Otherwise basic research showed most interesting effects of FRWBH to the perfusion, oxygenation and Interstitial Fluid Pressure of tumor tissue that could efficiently enhance the efficacy of radio- and chemotherapy. Clinical research about this approach has just begun at the Roswell Park Cancer Instute Buffalo.

Especially the time-scheduling of FRWBH cannot be generally defined, but is dependant from the therapeutic contexte.

Keywords

Fever; whole-body hyperthermia; cancer; immunotherapy; chemotherapy

Oncothermia Journal 10:121-132 (2014)

Old and new facts about hyperthermia-induced modulations of the immune system

Benjamin Frey, Eva-Maria Weiss, Yvonne Rubner, Roland Wunderlich, Oliver J. Ott, Rolf Sauer, Rainer Fietkau, & Udo S. Gaipl

Department of Radiation Oncology, University Hospital Erlangen, Friedrich-Alexander University of Erlangen-Nurnberg, Germany (Received 10 January 2012; Revised 27 February 2012; Accepted 15 March 2012)

Old and new facts about hyperthermia-induced modulations of the immune system

Abstract

Hyperthermia (HT) is a potent sensitiser for radiotherapy (RT) and chemotherapy (CT) and has been proven to modulate directly or indirectly cells of the innate and adaptive immune system. We will focus in this article on how anti-tumour immunity can be induced by HT. In contrast to some in vitro assays, in vivo examinations showed that natural killer cells and phagocytes like granulocytes are directly activated against the tumour by HT. Since heat also activates dendritic cells (DCs), HT should be combined with further death stimuli (RT, CT or immune therapy) to allocate tumour antigen, derived from, for example, necrotic tumour cells, for uptake by DCs. We will outline that induction of immunogenic tumour cells and direct tumour cell killing by HT in combination with other therapies contributes to immune activation against the tumour. Studies will be presented showing that non-beneficial effects of HT on immune cells are mostly timely restricted. A special focus is set on immune activation mediated by extracellular present heat shock proteins (HSPs) carrying tumour antigens and further danger signals released by dying tumour cells. Local HT treatment in addition to further stress stimuli exerts abscopal effects and might be considered as in situ tumour vaccination. An increased natural killer (NK) cell activity, lymphocyte infiltration and HSP-mediated induction of immunogenic tumour cells have been observed in patients. Treatments with the addition of HT therefore can be considered as a personalised cancer treatment approach by specifically activating the immune system against the individual unique tumour.

Keywords

Hyperthermia, heat shock proteins, dendritic cells, immunogenic tumour cell death, abscopal effects

Introduction

Hyperthermia (HT) is a clinical treatment for malignant diseases, in which tumour tissue should be heated to minimum temperatures of 40-41 C for a sufficiently long period of time. HT has been proven to modify blood circulation thereby delivering oxygen into the tumour tissue, to result in increased metabolism leading to reduced ATP levels and increased anaerobic metabolites, to foster protein aggregation aggravating DNA repair, to sensitise tumour cells for radio- and chemotherapy, and to modulate the immune system (summarised in Schildkopf et al.). However, talking as radiation immune biologists about HT nearly always evokes divided reactions. This is mainly due to contradictory published results ranging from immune activation to immune suppression induced by HT. The inconsistent outcomes after HT are often due to different temperatures and exposure times used for the experiments. We will outline in this review old and new facts about how HT modulates the immune system and will carve out factors responsible for mmune activatory modes of action of HT treatment. As hour of birth of immune therapy is often regarded the treatment of cancer patients with Coley's toxin, developed by Sir William Bradley Coley at the end of the 19th century. Killed bacterial cultures were directly injected into the tumour or the blood stream evoking strong fever with resultant spontaneous tumour regressions

observed in some patients. Those findings merit a place in history, but also in the present and the future. We will outline that 'historic results' have many implications for the future of HT as an additional element for anti-cancer therapy by inducing, besides many other effects, anti-tumour immunity, most pronounced when combined with radiotherapy (RT) and/or chemotherapy (CT) or further immune therapies (IT).

In the beginning of the 20th century many studies on the pathogenesis of fever were carried out and the linkage to cells of the innate immune system was made. It was discovered that fever in response to exogenous agents is mediated by a host phagocyte product called endogenous pyrogen (EP). Pyrogenes are released by phagocytosing granulocytes and stimulate immune responses. EP was later found to be identical to interleukin (IL)-1, being a powerful immune stimulator. Such findings suggest a strong relationship between fever, heat and immune responses. HT was further found to affect metabolism and membrane potential of innate immune cells (granulocytes). Rosen suggested that increased body temperatures after HT lead to modifications of cellular membranes; the tumour cell loses its 'random properties'. He concluded that HT increases the efficacy of the immune system. The latter might be the main mediator of the abscopal effects observed after distinct settings of HT treatment. Before summarising the literature on immune modulations induced by whole body HT (WBHT) and local HT (LHT) application, we will briefly introduce the immune system.

Basics about innate and adaptive immunity

An immune response can be divided into two main phases, namely an initial non-specific phase (innate immunity) mediated by granulocytes, monocytes, immature dendritic cells (DCs), natural killer (NK) cells, and soluble factors such as cytokines and a later specific phase (adaptive immunity) mediated by cellular (T lymphocytes) and humoral (B lymphocytes) immune reactions. The initial innate immune response uses germline genes to recognise foreign substances or damaged tissue. The adaptive one utilises somatically rearranged genes to generate multiple structural specificities that allow the induction of responses specific to individual invading organisms and damaged cells (modified from Colaco). It has become clear that these two responses are integrated in the response to an infectious organism and to 'danger' in the body. DCs were discovered by the Nobel Prize in Physiology or Medicine 2011 laureate Ralph Steinman, being the antigen presenting cells (APCs) as the site of this integration.

The innate immune system

Cells of the innate immune system act as first line defence against invading pathogens. Via pattern recognition receptors (PPR) on the surface of phagocytes (monocytes, macrophages, granulocytes, immature DCs), pathogen-associated molecular pat-terns (PAMP) such as lipopolysaccharide (LPS) are recognised. After binding to receptors, such as Toll-like receptors (TLR), the pathogens are engulfed by phagocytes. The latter secrete cytokines initiating inflammation and the induction of adaptive immune responses. Like PAMP, damage-associated molecular patterns (DAMP) are capable of active immune responses in a similar way (Figure 1.). DAMP result from damaged cells, for example, after exposure of tumour cells to RT and HT.
Besides phagocytes, NK cells belong to the cellular innate immune defence system. They possess activating and inhibitory receptors and recognise virus infected or tumour cells often displaying a reduced MHC class I surface expression.

The adaptive immune system

In contrast to non-MHC restricted tumour cell recognition by NK cells, the triggering of adaptive immune responses requires uptake and presentation of antigen via MHC molecules by APCs. DCs are immune cells connecting innate and adaptive immunity and belong to the group of APCs. After

recognition, uptake and processing of tumour antigen (Ag) resulting, for example, from damaged tumour cells, DCs mature and migrate into the lymph nodes (LN) to present peptides of tumour-associated Ag on their MHC complexes, express costimulatory receptors and secrete cytokines to prime naive CD4+ and CD8+ T-lymphocytes against the presented Ag (Figure 1.).

Antigens derived from intracellular sources such as viruses are presented on MHC class I to CD8?T cells whereas extracellular-derived phagocytosed material such as tumour peptides/Ag are usually presented on MHC class II to CD4+ T cells. However, the latter mentioned material can also be cross-presented on MHC class I molecules, a prerequisite for priming of CD8+cytotoxic T cells (CTL). CTL expand and traffic from the LN to the tumour where they exert their killing function. Importantly, efficient cross-presentation of tumour Ag requires both Ag uptake and a maturation signal for DCs resulting from, for example, necrotic tumour cells. Heat shock proteins (HSPs) comprise both functions by delivering tumour Ag and fostering maturation of DCs. DCs pulsed with heat shocked tumour cells mediated a significant enhanced CD4?8?cellular cytotoxicity response against the tumour cells compared to pulsed DCs with lysates of non-heat shocked cells. It has to be stressed that adaptive and innate immune responses complement each other. When tumour cells shed MHC class I molecules to escape killing by CTL, NK cells are activated against the tumour since inhibitory receptors are no longer triggered by MHC I molecules. Furthermore, a cross-talk between NK cells and DCs exists. As example, NK cells were shown to foster the maturation of DCs and DC-NK cell contact promotes NK cell proliferation Since hyperthermia in febrile (38-41 °C) or tumour therapeutic (41 °C) ranges is known to modulate interactions between the host immune and the tumour cells (summarised in Tomasovic and Klostergaard), we focus in the following sections on how WBHT or LHT modulate innate and adaptive immune responses.

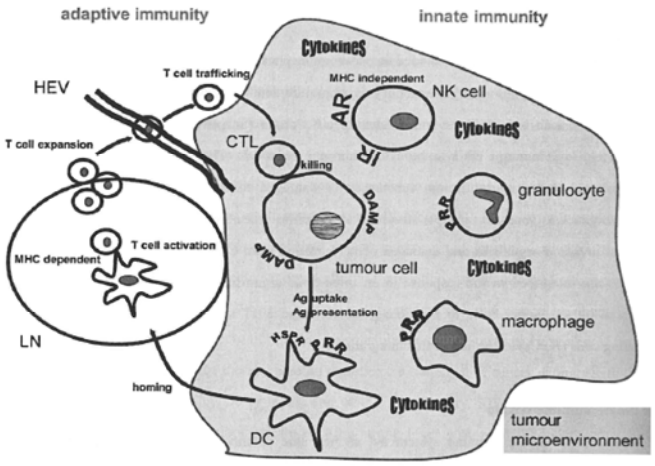


Figure 1. Hyperthermia modulates innate and adaptive immune responses

A general scheme of the main cells of the innate and adaptive immune systems that are involved in anti-tumour responses and can be modulated by hyperthermia is displayed. Heat damaged tumour cells expose damage-associated molecular patterns (DAMP) and can be recognised by innate immune cells via pattern recognition receptors (PRR). Natural killer (NK) cells are activated against the tumour via triggering activating receptors (AR) and inhibiting inhibitory receptors (IR) via MHC loss of the tumour cells. A beneficial cytokine milieu is created in the tumour microenvironment when innate immune cells are exposed to heat. Dendritic cells (DC) link the innate and adaptive immune response and take up heat shock protein/tumour antigen (Ag) complexes by way of heat shock protein receptors (HSPR). DCs present the tumour Ag to T cells and heat induces maturation and migration of DCs to lymph nodes (LN). There, T cells are activated in a MHC-dependent manner. They expand and traffick to the tumour cells by passing through high endothelial venules (HEV). Finally, the tumour cells are attacked and killed by the

activated CD8?T cells (cytotoxic T lymphocytes, CTL). As outlined in detail in the text, hyperthermia fosters in vivo all of the presented immune mechanisms against the tumour cells.

General effects of HT on innate and adaptive immune responses

Many studies have been carried out analysing the effect of WBHT on immune cell subsets. Of note is that local tumour treatments might also directly affect immune cells, since mononuclear leukocytes are commonly present in a heated tumour or in the surrounding tissues. For this reason, researchers started to examine the effects of HT on macro-phages. The response of macrophages to phytohae-magglutinin (PHA) measured by tritiated thymidine incorporation was enhanced when fever-range heat (38.5°C) was added while influenza virus depressed the macrophages' responsiveness. An enhanced production of virus-induced interferon by HT might be the cause of the beneficial effect of HT on responsiveness of influenza virus-exposed monocytes. Also lymphocyte transformation, mitogenesis, in response to PHA is temperature dependently influenced. Furthermore, IL-l induced T cell proliferation was found to be increased by HT. This systemic activation of the immune system might contribute to target metastatic tumour cells by HT (summarized in von Ardenne). Another hint for the induction of anti-tumour immunity by heat is given by the fact that migration of Langerhans cells (DCs of the skin) is influenced by WBHT and that DCs primed with Toll-like receptor-agonists respond to HT (39.5 ^{o}C) with significant increased IL-12p70 secretion. This is the main cytokine that drives TH1 polarisation. In general, heat induces an up-regulation of TLR4 on DCs and macrophages. In addition, HT in the fever range (38-41 °C) resulted in in vitro experiments in a highly significant increase in L-selectin-dependent adhesion of these cells to LN high endothelial venules (HEV) and stimulates lymphocyte homing to secondary lymphoid tissues. This is mediated by an increased expression of L-selectin and alpha4beta7 integrin on circulating lymphocytes. They then interact specifically with HEV.

Modulation of NK cells by HT

The modulation of NK cells by WBHT is a double-edged sword. NK cell activity was found to be decreased at higher temperatures in several in vitro assays. However, NK cell activity was observed to be enhanced by HT in vivo indicating that additional factors such as interferons resulting from latent infections contribute to the immune stimulating activity of heat. WBHT with 40.5°C resulted in decreased burden of lung metastases in mice, and NK cells were found to be involved in those anti-tumour effects induced by HT. In xenogeneic tumour models with SCID mice, host NK cells and injected human NK cells were enriched at the tumour site after HT treatment. NK cell depletion led to highly reduced amounts of dead tumour cells after HT. However, WBHT also suppresses the granzyme B/perforin NK cell mediated killing of tumour cells.Nevertheless, combination of WBHT with stimulation of NK cells by alpha-galactosylcer-amide ligand significantly retarded tumour progression and enhanced survival of the mice. A summary of how HT modulates NK cell activities was published some years ago by Repasky and colleagues.

Modulation of granulocytes by HT

Several studies prove that even locally applied HT activates the innate immune system. HT increases the amount of neutrophilic granulocytes. Giving granulocyte colony stimulating factor (GCSF) in addition, a significant enhanced anti-tumour activity mediated via active oxygen species generation by neutrophils was observed in preclinical mouse models. Granulocytes displaying anti-tumour activity were enhanced in tumours after HT. This recruitment into the tumour could be also enhanced by addition of GCSF. Furthermore, an increase of the bactericidal

capacity of granulocytes at 40°C and 42°C relative to 37°C was observed for many, but not all bacteria. However, higher temperature did not influence, at least in the applied in vitro systems, bactericidal capacity of macrophages. The authors concluded that HT enhances certain host defence mechanisms. Furthermore, peritoneal macrophages were not functionally suppressed or injured by microwave hyperthermia in vivo.

Modulation of T and B cells by HT

In a similar manner to NK cells, beneficial and non-beneficial effects of heat on T cells were observed. HT resulted in a reduced in vitro cytolytic activity of CTL. Besides T cells, B cells are modulated as cells of the adaptive immune system by HT. In vivo, B lymphocytes are more susceptible to heat damage compared to T cells. However, this is only observed during the treatment, and many in vitro experiments were carried out just giving heat directly to the immune cells. In vivo, immune cells can recover and may interact with the immunogenic cells induced by HT. Heat induced transient lymphopenia in serum can even result in elevated levels of T and B cells in the spleen. T cells might migrate from the blood into tissue and come in contact with Ag. Experiments with immune deficient and silica (known to suppress macrophage function) injected mice and rats revealed that an activated macrophage-antigen-T cell processing is necessary for complete tumour cell destruction and systemic tumour control by local HT application. HT further enhances Fas-ligand mediated T cell cytotoxicity via over-expression of heat shock factor-1 (HSF-1). Fas-L is a type II transmembrane protein able to trigger cell death by binding to its Fas receptor (CD95). The expression of CD95 by tumour cells may enable their killing by T cells via CD95/Fas-L-dependent mechanisms. Figure 1 schematically summarises the plethora of cells of the innate and adaptive immune system that are directly and/or indirectly activated by HT. In general, starting from fever-like conditions (39°C), the immune cell activity of cancer patients is increased during heat application. High temperature short duration WBHT (41.8°C) enhanced the amount of lymphocytes, monocytes and granulocytes significantly shortly after treatment compared to low temperature, long duration WBHT (40°C). In addition to the duration of heat application, timing of WBHT application is crucial. Since heat fosters migration of Langerhans cells out of the skin, it should be applied after another stimulus. In this scenario, migrating DCs are capable of delivering Ag to the LN. The beneficial effects of WBHT accentuate the additional mechanism of killing of cancer cells directly by HT, as outlined below, and contribute to anti-tumour efficacy.

Direct tumour cell killing by HT contributes to immune activation

Overgaard's summary of the literature until 1972 indicated that tumour cells can be directly killed by HT with higher temperatures. Cavaliere and colleagues previously used temperatures of 42°C in their studies. Nowadays it has become clear that heat-mediated cell killing may result in immune stimulation. Early studies already revealed that the immunogenicity of the tumour cells can be increased by HT. Repeated local HT treatment of tumours resulted in significant reduction in the weight of retroperitoneal metastases in a mamma carcinoma model in rats. On the day of the HT treatment the tumours displayed necrotic areas and cellular injury. Some in vitro models have shown that Ag shedding of the tumour cells was fostered by HT. This again highlights that multiple tumour Ag should be accessible after treatment of tumours with HT, a scenario that can be achieved by induction of necrotic tumour cells with, for example, RT plus HT. HT further resulted in increased transcription of several tumour-associated Ag.

Non-beneficial effects of HT on immune cells are timely restricted

HT may also impair functions and counts of immune cells such as NK cells and monocytes. This effect is mostly time restricted (recovery usually after 48 h) and can be avoided by targeted

application of HT. Analyses of mRNA level on the effect of HT on immune cells within the tumour showed that the suppression in gene expression of a range of immune cells is only a transient phenomenon. Localised application of HT in a preclinical model with sheep resulted in an increased lymph flow and most importantly lymphocyte trafficking.
Local HT application on legs of mice resulted primarily in the suppression of NK cell activity. However, after 2 days the activity was partially recovered and even enhanced after another 5 days. Furthermore, the amount and density of Langerhans cells is increased after local application of HT on tongues of rats. A plethora of differences in beneficial and non-beneficial effects of HT are mostly due to varying heating times and stress conditions. It will be of great importance to focus in the future on distinct temperatures and heating times as well as efficient temperature controls. The thermal dose is mandatory (summarised in Milani and Noessner) and more complete time and temperature analyses in vitro and in vivo for various types of immune cells and end points are needed.

In the following we will go into detail how a local HT treatment finally acts systemically. One way this could happen is that HT-induced denaturation of proteins results in the unfolded protein response (UPR), in release of processed Ag bound to HSP, and finally to activation of T cells by those Ag presented by DCs (Figure 2.).

HT-induced HSP-dependent immune activation can dominate over thermo-tolerance

Before the 1980s HSPs were only known to chaper-one intracellular proteins after cell stress. Hsp70 may act as cell survival protein by inhibiting the permeabilisation of lysosomal membranes. It also protects tumour cells from monocyte cytotoxicity mediated by TNF. HSPs are highly conserved constituents of all kinds of pro- and eukaryotic cells and appeared for a long period of time only to be connected with thermotolerance. In addition, a simplified view that HT may lead to immune suppression via induction of thermotolerance in tumour cells and RT via destroying immune cells has been in the mind of clinicians, scientists and the public for many years. However, HSPs have to be regarded as double-edged swords.

Nowadays it becomes more and more evident that besides a general and timely restricted immune suppression, treatments with HT and/or RT may result in specific activation of the immune system by induction of distinct modifications of the tumour cell surface and distinct forms of cell death.
Extracellular HSPs are immunogenic 'New facts' about HSP-mediated immune effects arose with the key findings in the 1980s and 1990s that intracellular and inducible HSPs may become immunogenic when complexed with tumour peptides and that HSPs are also found outside the cells as well as located at the tumour cell surface. Viable tumour cells of a plethora of tumour entities expose Hsp70 on their surface. This represents a unique feature to discriminate them from non-cancerous cells. RT has been found to further increase the amount of Hsp70 on the surface of the tumour cells. Heat treatment also inducesexposure of Hsp72 on the tumour cell surface, thereby rendering the cell susceptible to lysis mediated by NK effector cells. Of note is that HSPs are not only increased at the tumour cell's surface after RT, but can also additionally be released.

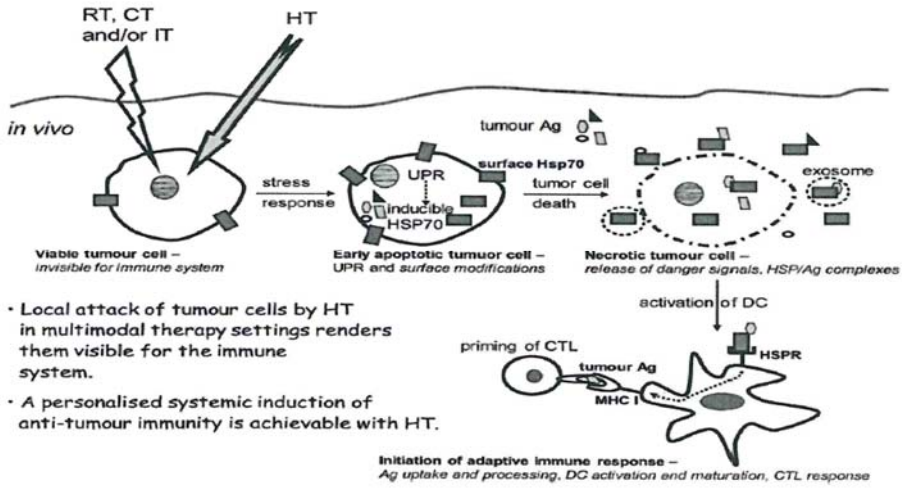


Figure 2. Hyperthermia modified tumour cells are rendered immunogenic and should be regarded as in situ tumour vaccine

When a tumour cell is heated, protein aggregation and denaturation induces a stress response in the cell, the so called unfolded protein response (UPR). Consequently, the transcription of inducible heat shock protein 70 (Hsp70) is increased and tumour cells expose even more Hsp70 on their surface. Furthermore, hyperthermia (HT) results in enhanced levels of tumour antigens (Ag) inside the cell. A second stress stimulus for the tumour cells such as ionising irradiation (radiotherapy, RT), chemotherapy (CT) or immune therapy (IT) together with HT fosters the induction of necrotic tumour cell death forms and modifies the tumour cell surface. Since necrotic cells have lost their membrane integrity, HSPs acting as danger signals and HSP/tumour Ag complexes are released. In addition, HSPs and tumour Ag containing exosomes can be discharged from apoptotic and necrotic tumour cells. Hsp70 containing exosomes derived from heat stressed tumour cells as well as HSP/tumour Ag complexes activate and attract dendritic cells (DC). The latter take up tumour Ag, present it with co-stimulation to CD8?T cells and thereby induce cellular anti-tumour immunity by priming cytotoxic T lymphocytes (CTL).

Increased serum levels of Hsp72 were detected in patients with prostate cancer. In addition, the expression of inducible Hsp70 correlates with increased tumour cell immunogenic properties when complexed with tumour antigens (discussed and summarised by Srivastava) by mediating antigen cross-presentation via MHC class I molecules. APCs utilise the uptake of HSP-chaperoned peptides for the loading of MHC class I molecules and thus stimulate a specific T cell response (Figure 2). Under oxidative stress, inducible Hsp70 was shown to be much more efficient in discriminating intracellular non-self-peptides than constitutive expressed Hsc70.The UPR occurs as a stress response towards heat and results in activation of the transcription factor HSFl which regulates the transcription of Hsp70. The UPR was found to be responsible for the generation of new antigenic peptides since oncoproteins have unique characteristics and are processed via the proteasome.

Besides direct effects, activation of the immune system by HT also involves indirect effects mediated through release of HSP and HSP/peptide complexes. The mechanisms of Hsp70-mediated and DC-dependent induction of specific tumour cell killing by cytotoxic CD8? T cells are summarised in Calderwood et al. Active and passive release pathways of Hsp70 have been described. Passive release by necrotic cells and the consecutive uptake of HSP/peptide complexes by DCs can lead to efficient T cell priming. The current knowledge about the release of HSP by cells with intact membrane is based on the fact that intracellular Hsp70 is located in cholesterol-rich micro-domains and binds to globotriaosylceramide (Gb3). It might be shuffled to the outside of the cellular membrane via regular flip-flop mechanisms.

Released Hsp70 is often associated with exosomes

Hsp70-containing exosomes derived from heat stressed tumour cells have just recently been discovered to activate and attract DCs and T cells also via the chemokines CCL2, CCL3, CCL4, CCL5, and CCL20. HSPs interact with multiple surface receptors of APCs, such as CD91, LOX1, CD40, and TLR, thereby inducing the secretion of immune activatory cytokines. Released HSPs are therefore regarded as a danger signal that stimulate many steps in the induction of innate and adaptive immune reactions from DCs up to CTL activation (Figure 2.). Members of the Hsp70-related Hsp 110 family cooperate with Hsp70 in protein folding in the cytosol. ·

Heat-inducible proteins can be rendered more immunogenic by pre-treatment with heat, while heat-insensitive proteins were not modified in their vaccination efficacy. Hsp 110 prepared from mice treated with WBHT were significantly better vaccines compared to those proteins isolated from non-heat treated animals. The authors concluded that Ag presentation pathways might be influenced by HT.

HSPs are induced in target/tumour cells as well as in APCs. HSPs are part of intracellular aggregates with cytoskeletal proteins such as spectrin in immune cells. An exposure to mild HT (40°C) has the same effect on localisation changes of those aggregates within the cells as other stimuli leading to lymphocyte activation. DCs exposed to heat up-regulated Hsp70 and concomitantly the co-stimulatory markers CD80, CD83, and CD86. In addition, a significant increased capacity of heat stressed DCs to prime CD8?T cells was observed. Fever-like temperature further leads to increased expression of Hsp90 in immune cells and thereby induces maturation of DCs. Since HSPs are strongly induced by thermal stress and their expression is only weakly modulated by electromagnetic fields, the current notion is that heat acts as main stimulator of HSP expression and immune stimulation.

The exposure of Hsp70 on the tumour cell surface serves as a recognition signal for activated NK cells. SCID/beige mice are deficient for T and B cells and lack additionally functional NK cells. In those mice the growth of Hsp70-over-expressing tumours was not reduced compared with control tumours. In contrast, in SCID mice (having functional NK cells) bearing Hsp70-over-expressing tumours, NK cells were activated and killed tumour cells ex vivo that expressed NKG2D ligands. The migratory and killing activity of NK cells was found to be stimulated by Hsp70 positive exosomes derived from tumour cells. In general, the activity of NK cells can be increased by up-regulation of activating receptors and down-regulation or blocking of inhibitory ones. Heat also up-regulates Hsp60 that binds to HLA-E MHC molecules. This complex is no longer recognised by CD94/NKG2A inhibitory receptors.

Taken together, cells of the innate (NK cells and DCs) and of the adaptive (CTL) immune system become activated by heat stress induced Hsp70. Importantly, the necessity of a cross-talk between NK cells and DCs for the induction of specific anti tumour immune responses becomes more and more clear and Hsp70 is one mediator of this cell-to-cell contact-dependent interaction. For example, Hsp70 induced the expression of the NKG2D ligand MICA (the MHC class I chain-related protein A) on DCs.

Immunogenic tumour cell death induced by combinatory treatments with HT

Many additive and even supra-additive anti-tumour effects have been described when combining RT with HT. As one example, HT increases the blood flow and thereby improves tumour tissue oxygenation leading to a better outcome of RT. The complementary modes of action of RT and HT are summarised in Schildkopf et al. and van der Zee. One major factor of the enhanced

radiosensitivity of tumour cells after heat application is the inhibition of the repolymerisation step in the repair of base damages induced by RT. Just recently it was demonstrated that HT induces Breast Cancer 2 susceptibility protein (BRCA2) degradation and thereby inhibits homologous recombination. Besides radiosensitisation based on interference with cellular DNA, combinatory treatments of RT and HT may result in immune activation against tumour cells that have been modified by the therapy.

Combination of RT with HT induce immunogenic necrotic tumour cells

Modification of the tumour cell surface or the release of danger signals via damaged tumour cell membranes may render the tumour cells as visible targets for immune attack. Heated cells modify their surface in many ways, like that antibodies bind differently. HT treatment (43.5°C) enhanced cytotoxicity by antibodies mono-specific to a certain tumour Ag, suggesting that HT is capable of augmenting specific immune reactions against tumour-associated cell membrane Ag. Fresh spleen cells of mice inoculated with heat-treated tumour cells (42°C for 30 min) showed a clear tumour-neutralising activity. Tumour cells that are exposed to two stress stimuli, such as RT and HT, die of apoptosis and necrosis. Heat-induced apoptosis is mediated via caspase-9. Besides apoptotic cells, forms of programmed necrosis can also be induced in tumour cells after HT, RT or HT plus RT. Therefore, some effects of HT lie in killing of tumour cells and consecutive activation of the immune system. Already in the 1970s, Muckle and colleagues suggested that mode and form of tumour cell death and consecutive uptake of necrotic tumour cell material following treatment could be important in enabling the host to deal with metastatic cells. This indicates that local RT and HT treatment can induce systemic immune-mediated effects. Induction of tumour cell necrosis by local HT with 42°C resulted in complete disappearance of the tumour in one half of the mice. A long disease-free survival of the mice was observed (up to 18 months) suggesting that HT led to systemic tumour control. Of note, the non-surviving animals had defective immune systems. At temperatures below 41°C no necrosis occurred, whereas at temperatures between 42 and 45°C an increased rate of necrosis is observed. Necrotic cell death with release of danger signals can be induced by HT and finally leads to cross-priming of tumour Ag by DCs. In contrast, a chronic enhanced level of HMGB1 fosters inflammation, angiogenesis, evasion of cell death, and metastases. Of note is that even a resistance to tumour growth can be stimulated by pre-treatment of mice with two stimuli (heat plus X-ray) before tumour inoculation. In this model, the resistance was independent of T cells, as revealed by experiments with nude mice. One has not to conceal that WBHT with lower temperatures was not effective in inducing anti-tumour immunity and even led to compensation of anti-tumour immune responses triggered by whole tumour cell vaccines.

Combinations of cytokines with HT induce immune activation

Researchers and clinicians became even more aware in the 1980s that cancer is a complex disease not only related to the tumour cells themselves. To treat the very heterogeneous neoplastic diseases, a multimodal approach should be followed consisting of surgery, radiotherapy, chemotherapy, immunotherapy and/or HT. How HT enhances the cytotoxicity of chemotherapeutic drugs at multiple levels is excellently summarised by Issels.

The most prominent anti-tumour effect in mice bearing Lewis lung carcinoma was observed using IL-2 therapy combined with local HT. A beneficial targeting of metastatic tumours was also achieved with combinations of IL7, being important for B and T cell development, and HT. HT actually abrogated the inflammatory and thereby anti-immunotherapeutic effect of IL-8. Application of HT with a further trigger results in increased TNF-alpha levels secreted by macrophages. Distinct sequences for macrophage triggering or treatment of tumour cells with tumour necrosis factor plus application of HT is capable of augmenting the cytotoxic actions of

macrophages against the tumour cells. HT leads to fast, significantly increased, but timely restricted secretion of cytokines such as TNF-alpha and IL-l-beta fostering early activation of host defence immune mechanisms. This timely restricted pulsing of the immune system induced by HT is comparable to the new facts of action of HT where HMGB1 is released from tumour cells after RT plus HT. Combination therapies such as adding TNF-alpha to HT also resulted in massive tumour cell necrosis. As mentioned before, the pulsatile release of danger signals such as HMGB1 by necrotic cells fosters cross-presentation of Ag by DCs.

Taken together, especially combinations of HT with further stimuli may lead to efficient anti-tumour immune responses. Sublethal damages induced by CT or RT are rendered lethal by additional application of HT. This is again another important reason for the recommended combined cancer treatment with HT plus RT and/or CT. In preclinical models it has been shown that HT added to RT increases local tumour control rates from 25% up to nearly 90%, but also systemic tumour control is improved by combination of HT plus RT, as proven by longer survival rates of the patients.

Combination of HT with further immune therapies induce immune activation

Very effective anti-tumour responses were observed in preclinical models when HT was combined with further immune therapy, namely injection of DCs. DCs were activated and matured by Hsp70. In addition, HSPs fostered an increased CTL and NK cell activity. DCs loaded with melanoma cells that were heated to 42°C before killing were more efficient in priming of naive CD8?T cells than DCs loaded with unheated melanoma cells, indicating that HT fostered cross-priming of tumour Ag by DCs. In addition, heat shocked DCs themselves were potent stimulators of cytotoxic T cell responses against thyroid carcinoma. Treatment with Flt3L (which induced proliferation of DCs) and local RT led to abscopal anti-tumour effects and to eradication of small lung metastases. The induction of abscopal anti-tumour immunity and immunogenic tumour cell death by RT and further immune stimulation was recently summarised by Frey et al.

DC activation after combined HT therapies as key inductor of anti-tumour immune responses

In conclusion, local HT can lead to local, but also to systemic tumour control. A prerequisite for the latter is the migration of DCs that have taken up tumour Ag to LN (homing). Increased expression of CCR7 and decreased expression of CCR6 on DCs are required for their functional migration to regional LN. Exactly this expression profile was observed on mRNA level for Langerhans cells after local HT and also on protein level after contact of DCs with supernatants of tumour cells that have been exposed to HT plus RT. The release of Hsp70 is significantly enhanced when HT is added to RT and extracellular Hsp70 is one main player in inducing DC maturation and homing. We have to stress again that the release of immune activatory proteins such as Hsp70 and danger signals such as HMGBl, which are normally located inside the cells, after local treatment with HT plus RT mediate abscopal anti-tumour effects (see below and Figure 2). Radiotherapy regimens and certain chemotherapeutic agents trigger forms of cancer cell death that stimulate an active immune response against the tumour. RT plus HT stimulates the DC-mediated CTL response against the tumour, but also increases the expression of activating NKG2D ligands for NK cells on tumour cells thereby activating innate immune defence mechanisms. The number of cytotoxic T cells and NK cells is significantly increased after local HT treatment of melanoma in mice. In addition, increased amounts of activated monocytes (CD11b? CD69?) were present in the tumour microenvironment after HT.

Local HT applications result in systemic immune activation

First hints for an activation of the immune system after local tumour treatments were the improved survival times of patients with melanoma. A combination of IL-2 and local HT was beneficial in preclinical models for certain metastatic tumours. Tumour cells with high metastatic potential were more sensitive to HT treatment and the survival rate of mice bearing metastatic B16-F10 tumours was increased after HT. Infiltration of NK cells and macrophages into the tumour, containing necrotic melanoma cells induced by HT, takes place after local HT treatment. Notably, the addition of rIFN-beta to HT had no effect on NK cell infiltration but significantly increased the amount of T cells in the tumour. In another preclinical study using the MCA-105 sarcoma metastatic cell model, WBHT in adjunct to immune therapy had no significant effect on tumour growth.

However, the combination of LHT and immune therapy with lymphokine-activated killer cells significantly decreased the number of pulmonary metastases. LHT in addition to further stress stimuli might be considered as an autologous in situ tumour vaccination, as it is also true for RT combined with immune activators such as AnxA5. Zhang and colleagues recently summarised in detail how LHT alone and more importantly in combination with further immune therapy or RT is capable of rendering tumours immunogenic in situ. Immune defence mechanisms have always to be considered for the treatment of small tumour masses, recurrent tumours, metastases and micrometastases (being not displayed by current imaging techniques). Combinations of RT, CT or surgery with HT kill two birds with one stone: the primary tumour is reduced in size by the RT, CT or surgery, and residual tumour masses and metastases are killed via immune activation with the addition of HT (Figure 2.).

HT activates systemic anti-tumour immune responses in cancer patients

HT and immunity fit together. The clinical effectiveness of HT treatment in multimodal settings is described in detail in other papers of this special issue. Many randomized clinical trials have proven the effectiveness of HT when combined with RT, RCT, or CT. Recently, a randomized phase III multi-centre study has demonstrated that regional HT significantly increases the benefit of CT in adult cancer patients with high-risk soft-tissue sarcoma. In the following we briefly mention some further studies clearly indicating that application of LHT and WBHT mostly in addition to RT and/or CT contribute to systemic tumour immune defence mechanisms. Patients with advanced adenocarcinoma of the prostate receiving local HT treatment displayed a significant NK cell cytotoxic activity when compared to the pretreatment status. An increased NK cell activity after local HT application was even observed in patients with liver cancer, being a tumour hard to treat with HT because of its high perfusion. Preoperative radio-chemotherapy combined with local HT led to an increased lymphocyte infiltration and increased survival rate of patients with oesophageal cancer compared to radio-chemotherapy treatment alone. A prolonged T cell activation was observed after WBHT at higher temperatures (41.8 ^{o}C) in addition to CT in patients with metastatic colorectal carcinoma. Currently, combinations of HT with DC-based immune therapy are tested for therapy of squamous cell carcinoma. Without RT, a three-step therapy setting (HT with 43 ^{o}C and 41 ^{o}C and DC vaccination) seems to be most beneficial in inducing anti-tumour immunity.

In cervical cancer, a study comparing RT with RT plus HT revealed that the percentage of patients with continuing pelvic control developing metastatic disease was significantly lower in the group with combined treatment. This might be due to the HSP-mediated induction of immunogenic tumour cell death. Clinical trials using HSP/ peptide complexes have been carried out. Patients showed a longer disease-free survival indicating that systemic anti-tumour immune responses were induced. HSPs become hyperabundant under stressful conditions. We emphasise that HSPs

induced by HT may contribute to anti-tumour immunity. Smaller tumour masses in early stage diseases or metastases are attacked by those immune-mediated mechanisms.

A phase III trial showed that M1a and M1b stage IV melanoma patients receiving larger numbers of immunisation with autologous HSP gp96-peptide complexes survived longer compared to patients receiving fewer treatments. The clinical results are consistent with observations in mouse models examining the 'immunological power' of HSP-based vaccines. Another randomised phase III trial with adjuvant treatment in renal cell carcinoma revealed that patients in early stage disease have a hazard ration for recurrence of disease of 0.57 when receiving the HSP/peptide vaccine. Of note, both trials failed to meet their end points with respect to the intention-to-treat population (receiving the HSP/peptide vaccine). Nevertheless, retrospective subgroup analyses clearly showed that distinct groups of patients receiving multiple vaccinations significantly profited from the immune therapeutic 'vaccitherapy'.

Short outlook

Repeated in situ induction of HSP tumour peptide complexes by HT treatment in combination with strong death stimuli for the tumour cells such as ionising radiation might result in great clinical benefit in the future. The in situ induction or vaccination with autologous HSP tumour material applies the strong immunogenic potential of the unique tumour composition of each individual patient as therapeutic option. A personalized cancer treatment approach that takes into account the individually unique tumour composition is feasible by combining HT with further standard and immune therapies (Figure 2.). The temporarily restricted mode of modifying the tumour microenvironment by HT likely prevents the development of immunological tolerance. Hence, repeated HT treatment cycles included in multimodal therapy settings should be arranged. HT and induction of local and systemic anti-tumour immunity are things that have and still fit together even closer.

Declaration of interest: This work was supported by the German Research Foundation (GA 1507/1-1), the German Federal Ministry of Education and Research (BMBF; m4 Cluster, 01EX1021R and GREWIS 02NUK017G), and the European Commission's DoReMi, European Network of Excellence (contract number 249689). The authors alone are responsible for the content and writing of the paper.

Oncothermia Journal 10:134-145 (2014)

Biological Rationales and Clinical Applications of Temperature Controlled Hyperthermia - Implications for Multimodal Cancer Treatments

P. Shildkopf[1], O.J. Ott[1], B. Frey[1], M. Wadepohl[2], R. Sauer[1,3], R. Fietkau[1] and U.S. Gaipl[1]

(1) Department of Radiation Oncology, University Hospital Erlangen, Universitaetsstr. 27, 91054 Erlangen, Germany

(2) Dr. Sennewald Medizintechnik, Munich, Germany

(3) United Cancer Center, Erlangen, Germany

Oncothermia Journal 10:134-145 (2014)

Biological Rationales and Clinical Applications of Temperature Controlled Hyperthermia - Implications for Multimodal Cancer Treatments

Abstract

Hyperthermia (HT) - heating the tumor in the range of 40.0 - 44.0 ^{0}C - combined with radiation (RT) and/or chemotherapy (CT) is a well proven treatment for malignant tumors. The improvement of the techniques for monitoring and adapting of the desired temperatures even in deep seated tumors has led to a renaissance of, now quality-controlled, HT in multimodal tumor therapy approaches. Randomized clinical trials have shown improved disease-free survival and local tumor control without an increase in toxicity for the combined treatment. In this review, we will focus on biological rationales of HT comprising direct cytotoxicity, systemic effects, chemosensitization, radiosensitization, and immune modulation. The latter is a prerequisite for the control of recurrent tumors and micrometastases. Immunogenic tumor cell death forms induced by HT will be introduced. Modulations of the cytotoxic properties of chemotherapeutic agents by HT as well as synergistic effects of HT with RT will be presented in the context of the main aims of anti-tumor therapy. Furthermore, modern techniques for thermal mapping like magnet resonance imaging will be outlined. The effectiveness of HT will be demonstrated by reviewing recent clinical trials applying HT in addition to CT and/or RT. We conclude that hyperthermia is a very potent radio- as well as chemosensitizer, which fosters the induction of immunogenic dead tumor cells leading to local and in special cases also to systemic tumor control.

Keywords

Hyperthermia; radiotherapy; chemotherapeutics; immunogenic cell death; cancer, anti-tumor immunity; danger signals; magnetic resonance images

1. Effects of hyperthermia treatment on cells

Hyperthermia (HT) treatment describes the targeted and controlled heating of tumor tissues in the range of 40.0-44.0 ^{o}C. Various application techniques are used for treating cancer patients like local, interstitial, or regional hyperthermia and hyperthermic limb perfusion techniques. As a single treatment, the efficacy of hyperthermia alone is not enough to replace the conventional established cancer therapies (X-ray and chemotherapeutics), but it is known to induce thermal chemosensitization and thermal radiosensitization. The main aim of hyperthermia treatment is therefore the improvement of conventional therapies in multimodal cancer treatments. Further biological rationales of HT comprise direct cytotoxicity, systemic effects, and immune modulation, which will be elucidated in the following paragraphs.

1.1 Cytotoxic Effects of Hyperthermia

Since the early 70's, pre-clinical research with exponentially grown cells revealed the thermal dose, dependent on time and given temperature, being most critical for the induction of cell death and systemic effects. Temperatures ranging from 41 to 47 ^{o}C exhibited a direct cell killing effect in vitro and in animal hyperthermic experiments [2-4]. The survival curves after HT treatment show a two-step process of cell killing: in the beginning of heat exposure a linear growth arrest is

observed, followed by exponential cell death. A correlation between the thermal energy dose necessary to induce exponential cell death and the denaturation of cellular proteins was found in vitro. Therefore, the direct cytotoxicity of HT treatment seems to be based on the denaturation and aggregation of cytoplasmic, nuclear or membrane proteins, but similar relationships could not be detected for radio or chemosensitization phenomena.

1.2 HT Effects on Tumor Microenvironment

Malignant tumors are regarded as autonomous organs with specialized microenvironment, which is characterized by reduced blood flow and blood vessel density. Inside the tumor tissue this chaotic vasculature often leads to areas of acidosis, hypoxia and energy deprivation in form of ATP. These factors turn cells more sensitive to hyperthermia, especially in low perfused areas. Therefore, at temperatures between 40 and 44 ^{o}C hyperthermia induces an almost selective destruction of tumor cells in hypoxic and acidic parts of solid tumors in vivo, but leaves normal tissues intact.

1.3 HT Thermotolerance

When cells are exposed to various forms of stress, specific stress proteins are upregulated, which often fulfill functions as molecular chaperones and prevent lethal damage of the cells. In the case of hyperthermia, the proteins at least partly involved are heat-shock proteins (HSP), which might render cells transiently thermotolerant to further HT treatments, an undesirable side-effect in cancer therapy. However, following more intense or prolonged heat treatment, these compensatory mechanisms often fail to prevent tumor cell death.

2. Effects of radiotherapy on cells

Radiotherapy (RT) is one of the standard treatments anti-tumor therapy. RT can be given as an adjuvant or neoadjuvant treatment and its main function is the local control of tumors in cancer patients. Ionizing irradiation inflicts various types of DNA damage, but the subsequent production of DNA double-strand breaks (DSB) is thought to be the main damage after RT. Most of the DNA damage induced by RT occurs not in single DSB, but in clustered or bulky lesions with multiple DNA and base damages which exacerbate the proper repair for the cell.
The DNA damages induced by RT lead to a cell-cycle arrest in the G2/M phase, in which cells are highly susceptible to further irradiation, commonly utilized by fractionated RT. The fractionation scheme has been developed empirically over the last century and generally contains five daily treatments per week, mostly applying 1.8 -2 Gy per fraction.

Therefore, ionizing irradiation primarily leads to cell inactivation or to a proliferative stop rather than to direct cell killing, in contrast to chemotherapeutic agents. However, it has been shown that ionizing irradiation is capable of directly damaging mitochondria in cells, which may induce apoptosis. Furthermore, X-ray in a half-weekly or weekly cumulative dose of 5 or 10 Gy induces tumor cell death. We have just recently shown that necrosis is the prominent form of cell death in the days after irradiation of colorectal tumor cells.

Local tumor control, also termed radiocurability, is mainly achieved through the elimination of proliferating (clonogenic) tumor (stem) cells. Curability of a certain tumor cannot be predicted through local tumor control alone, because of each tumor's propensity for metastasis or recurrence. Radiotherapy as a single therapy is often not able to eradicate all clonogenic tumor cells. Therefore, radiotherapy is a local rather than systemic treatment modality which can improve patient survival but often needs additional treatments like chemotherapy and/or hyperthermia.

3. Effects of chemotherapeutics on cells

The primary cytotoxic mechanism of many conventional chemotherapeutic agents (including alkylating agents, platinum compounds, topoisomerase inhibitors and the antime-tabolites) is the emergence of DNA damage and the subsequent induction of cell death. All traditional cytostatic drugs lead to various side effects due to limited selectivity of the antitumor agents: leukopenia, mucositis, nausea, and vomiting.
The evolving field of chemotherapy in tumor treatment comprehends various clinical relevant classes of cytotoxic agents. In this review, we can only describe some chemotherapeutics exemplarily, which are also important in the combined use with hyperthermia.

3.1 Alkylating Agents

The alkylating agents (e.g. cyclophosphamide and ifosfamide) belong to the old-established anticancer drugs, which are still important for the treatment of various human cancers. Most of these agents are methylating (temozolomide) or chloroethylating (carmustine) active. In both cases 06-Guanine in DNA and RNA is an important cellular target, but also other sites are alkylated. Secondary effects of the alkylations are DNA-DNA cross-links, mismatches, and highly toxic DSB.

3.2 Platinum Compounds

For over 30 years, cisplatin has been a highly effective platinum-based anti-cancer drug that continues to play a central role in cancer chemotherapy. However, the use of cisplatin causes severe side-effects and various toxicities in patients. For this reason, new platinum compounds have been screened as potential anti-tumor drugs, less toxic than cisplatin but equally effective. Carboplatin and oxaliplatin have been approved for clinical use in 1989 and 2003, respectively.
In general, the accepted cellular target for platinum complexes is the DNA. Cisplatin cytotoxicity was thought to result from the inhibition of DNA synthesis. However, recent evidence indicates that cisplatin can kill cells by apoptosis.

3.3 Anthracyclines

The first anthracyclines (including doxorubicin) were isolated from Streptomyces bacteria in the 1960's. Doxorubicin has a broad antitumor spectrum, with numerous solid tumors in addition to haematological malignancies. Anthracyclines are still frequently used in clinical practice and in particular doxorubicin remains an important cytotoxic component for the treatment of many human cancers. Current clinical practice often combines anthracyclines with novel agents to maximize the therapeutic effect, instead of replacing them. The main cellular target of anthracy-clines is generally recognized to be topoisomerase-II. Inhibition of this enzyme blocks DNA replication as well as transcription. DNA strand breaks may trigger apoptosis of cancer cells via the p53 pathway.

4. Hyperthermia adds to radiotherapy

Ionizing irradiation and hyperthermia treatment act in a synergistic way, called thermal radiosensitization. Compared to HT alone, RT plus HT led to an increase in cell death even at lower temperatures. The thermal enhancement ratio (TER) defines the amount of thermal radiosensitization by the quotient of the survival fraction after X-ray alone and in combination with hyperthermia. The synergistic effects of HT and irradiation are mainly based on the complementary targets of both treatment modalities (Figure 1.).

Solid tumors may contain hypoxic areas because of diffusion- or reperfusion-limited oxygen supply. Hypoxic cells are two to three times more radioresistant than normoxic cells. Therefore, between fractionated doses of irradiation a certain time interval is needed to ensure reoxygenation of the tissue and to reduce the negative effect of tumor hypoxia on local control. Hypoxic areas in solid tumors represent a major therapeutic concern: the extent of hypoxic conditions in solid tumors has been shown to correlate with poor prognosis for the patient for different tumor types. However, hypoxic cells were shown to be highly sensitive to the combination of RT and HT. This may be due to increased vascularization and enhanced vessel permeability, with an increase in oxygen pressure levels in the tumor and the surrounding microenvironment after moderate HT treatment. To yield the highest synergistic effects between RT and HT, both treatments should be applied synchronously or after time intervals of 2-4 h. Hyperthermia alone may foster metastases but the combination with RT does not increase metastases and leads to systemic, immune activating effects.

During the cell cycle, the mitotic phase shows the highest heat sensitivity, but also S-phase cells are sensible to hyperthermia treatment. In contrast, cells in G2 phase are most sensitive to ionizing irradiation. The variations in heat sensitivity during the different cell cycle phases refer to the diversity of molecular mechanisms of cell death induction after HT. Additionally, hyperthermia affects the DNA repair, leading to increased radiation-induced chromosomal aberrations. The underlying mechanism of repair inhibition seems to be·alterations in chromatin organization, due to aggregation of nuclear proteins. The major effects of heat on radiosensitivity are suggested to work via inhibition of the repolymerisation step in the repair of base damages (base excision repair), which leads to the formation of secondary, toxic DNA double strand breaks. Taken together, HT is one of the most potent sensitizers for ionizing irradiation.

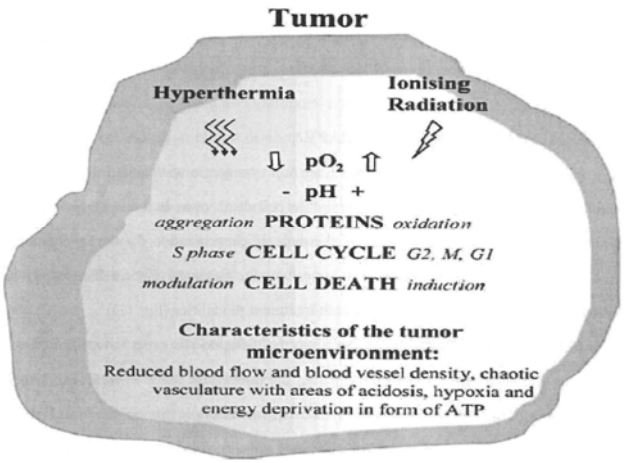


Figure 1. Synergistic mode of action of HT and RT. The tumor microenvironment is characterized by reduces blood flow and vessel density. This chaotic vasculature leads to areas of acidosis, hypoxia and energy deprivation in form of ATP. Radiotherapy (RT) and hyperthermia (HT) treatment act in a synergistic way, based on the complementary target functions of both modalities

5. Hyperthermia adds to chemotherapy

Hyperthermia is also capable of enhancing the cytotoxicity of chemotherapeutic drugs at multiple levels. The TER expresses the extent of a chemotherapeutics' thermal chemosensitization, as the quotient of cell survival at the elevated temperature and the normal temperature. The combination of HT and chemotherapy was shown to increase the inhibition of clonogenic cell growth both in vitro and in animal models. Chemotherapy and heat can interact in different ways. The platinum compounds (like cisplatin and oxaliplatin) and alkylating drugs (cyclophosphamide) show linear

enhanced cytotoxicity when temperatures are raised from 37 to 40.5 ^{o}C. Conversely, antimetabolites like 5 'Fluorouracil have not been found to interact with heat. This lack of interaction may still lead to an improved therapeutic result in vivo because spatial cooperation and/or toxicity independency may nevertheless exist. In vivo studies have demonstrated that the thermal enhancement of cytotoxicity is maximized at temperatures between 40.5 and 43 ^{o}C for many chemotherapeutic agents.

Possible mechanisms for the thermal chemosensitization include an increased rate of alkylation, an increase in drug uptake, and the inhibition of drug-induced sublethal or lethal damage repair. The distribution of cytostatic drugs in the tumor tissue may be further affected by changes in tumor blood supply and variances in fluid and electrolyte balance, as well as pH-changes that may lead to altered drug solubility and volume distribution. In cancer patients, the drug heat interaction appears to be much more dependant on these environmental factors mentioned than those of irradiation and heat. Clinically achieved temperatures are rarely high enough (> 43 ^{o}C) to cause vascular damage and it was found that HT between 40 and 43 ^{o}C causes increased tumor blood supply. The critical factors for drug uptake are blood flow and vascular permeability, which are both increased by hyperthermia treatment.

In general, studies on drug-heat sequence show that, the administration of drugs immediately before HT is most effective. However, exceptions like the antimetabolite gemcitabine exist, where a time interval of 24 h between drug and heat application has been needed to yield a synergistic effect in vitro and in vivo.

One further benefit of combining chemotherapy with HT is that cells with acquired drug resistance (often multifactorial) can be made responsive to drugs again. In particular, this mechanism of reverting drug resistance could be shown for cisplatin. Moderate HT treatment itself is not able to induce directly chromosomal DNA strand breaks but can alter the chromatin structure, thus influencing DNA repair. When combined with heat, chemotherapy behaves similar to X-ray: heat appears to convert sublethal damage to lethal damage, which reduces the expression of malignant transformation.
The combination of chemotherapy and hyperthermia may not only be advantageous for the treatment of primary cancers, but may also result in a lower risk of treatment-induced secondary cancers. Table 1. displays exemplarily possible mechanisms how HT is capable of increasing the efficacy of certain classes of chemotherapeutic agents. How HT adds to many chemotherapeutics has been just recently overarchingly reviewed by Dr. Issels.

6. Technology for application and monitoring of hyperthermia

For heating of superficial and deep seated tumors many methods have been developed and studied in past. During the 80's of the last century, many home-made and commercially available hyperthermia systems were in clinical use.

Class of agent	Name	Cellular target	Mechanism
Platinum drug	Cisplatin	Membranes and DNA	Increased drug uptake, increased DNA-adducts and protein binding, incrased cell death
Alkylating agents	Cyclophosphamide Mitomycin	DNA strand breaks DNA	Increased rate of alkylation Increased radical production
Antibiotics	Doxorubicin Mitoxantrone	Membranes and DNA	Increased drug uptake, increased drug half-life, increased oxygen radical production Increased drug uptake, increased inhibition of topoisomerase II

Table 1. Modulation of Cytotoxic Properties of Chemotherapeutics by HT

However, not all of them were capable of heating the target regions up to the desired temperatures. Electromagnetic energy (microwaves for superficial tumors and radiofrequency of deep heating) has been shown to be more suitable than other methods like ultrasound. Ultrasound used for thermal ablation (high intensity focused ultrasound) of small lesions has some disadvantages (e. g. reflections at bone structures, cavitation at air filled gaps) in heating larger volumes.

For the delivery of electromagnetic energy to the tumor tissues, two basic methods are used: radiative antennas and capacitor plates. Systems using capacitor plates are not able to steer the distribution of the energy. The energy absorption in the tissues between the plates depends on the characteristics of the tissues and is modified by blood perfusion. Therefore, overheating of poorly perfused fatty tissues is very common by using this technology and selectively heating of deep seated tumors is not possible. Hyperthermia systems with radiative antennas are used for superficial and deep heating. For superficial heating, waveguide or spiral antenna applicators are used. To increase the heating patterns for treatment of large lesions (e. g. breast wall recurrence of breast carcinoma) multiple antenna applicators have been developed. The penetration depth of systems for superficial heating is limited to 3 to 5 centimeters.

Selective deep heating of tumors is possible using radiative antenna arrays. Dipole antennas or waveguide applicators are placed around the body part containing the tumor. By steering amplitude and phase of the electromagnetic waves radiated from the antennas, a constructive interference is created at the target zone (tumor region). This means that high density electromagnetic fields are present in the tumor region. The energy of those fields is transformed into heat.

Monitoring of the temperature in the tumors and the surrounding tissues is mandatory. Because of the blood flow and its variations caused by the increased temperature, a homogeneous heating of the tumor region is not very likely. Therefore, the temperature of the tumor and the surrounding tissue cannot be predicted or calculated and must thus be measured. Temperature measurements can be performed by temperature probes or non-invasive methods. Temperature probes can be inserted into the human body either in natural orifices or percutaneously. In clinical practice, blindended plastic catheters are placed in and near the tumor region. Temperature probes are inserted in these catheters to measure the temperature. A continuous measurement is possible by using probes that are non-disturbed by electromagnetic fields. To get more temperature information, the probe can be mechanically moved along the catheter tracks. The use of multi-sensor probes is also possible. However, the temperature information obtained by those methods is rather limited. A lot of non-invasive methods for temperature mapping have been studied. Temperature maps derived from magnetic resonance images (MRI) have been shown to be a practical method in clinical routine and is used by a hybrid system for temperature-controlled hyperthermia (Figure 2.).

The method uses the temperature depended shift of the proton resonance frequency. This shift is included in the phase images acquired with a gradient echo sequence. By subtracting the images from a basal ("cold") image data set, the changes in proton resonance frequency can be recalculated into temperature changes. Part of the changes in proton resonance frequency is not caused by changes in temperatures but in perfusion. However, the comparison between MRI temperature measurements and temperature probe measurements showed a very good correlation. The resulting data set is color-coded (blue- cooler, green no change, orange, red and yellow-hotter) and superposed in the MR images. After some error corrections (e. g. drift of the static magnet field of the MRI system) the images are displayed as a temperature map in a three-dimensional data set. The temperature resolution is about 0.5 ^{0}C. Since this method has some disadvantages in clinical routine (e.g. movement of the patient creates artifacts) other methods like true T1 imaging or spectroscopy methods are under investigation.

7. Cancer and immune system – immune modulation by hyperthermia

Immune Evasion

Pre-malignant or mutated cells are normally removed efficiently by the immune system. It is well known that mice lacking essential components of the immune system get more susceptible to develop spontaneous tumors. Cancer cells have evolved manifold mechanisms to avoid the so called immunosurveillance, reviewed in. This seventh hallmark of cancer, to escape innate and adaptive immune responses, is conducted through immunoselection (selection of non-immunogenic tumor cell variants) and immunosubversion (active suppression of the immune response). Data from various human studies support the system of cancer immunosurveillance, which includes CD8+ T-cells, TH1 cells, NK cells, the local suppression by Tregs, and different tumor-cell products.

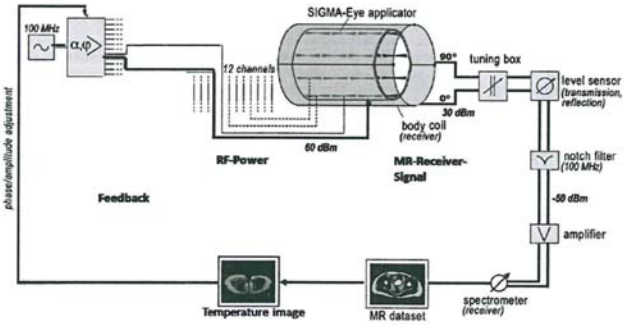


Figure 2. Schematic diagram of a hybrid system for temperature-controlled hyperthermia

The hybrid system consists of a hyperthermia system (BSD 2000/3D-MRI) and a magnetic resonance tomograph (Siemens Magnetom Symphony). This new technique provides the quality-assured heating of tumor tissues, even in deep seated malignancies. Modified according to Wust et al.

7.1 Ionizing Irradiation and Immune System

Besides the targeted effects of X-ray (DNA-damage) described in section 2, so called non-targeted effects exist, which influence "bystander" cells that received no irradiation themselves. This bystander effect may be conducted through genomic instability transmitted to the cell's progeny over generations or through various damage signals transmitted by irradiated cells to non-irradiated cells. Similar effects have been described for the abscopal effect, which is also called distant bystander effect. It describes the phenomenon that local irradiation of a specific body part results in a systemic outcome that is caused by the immune system. The involvement of the immune system could also be shown by in vivo experiments, in which irradiated immune competent mice showed tumor regression, whereas immune deficient nude mice showed tumor progression.

Immunogenic Cell Death

Because of the immune evasion of malignant cells, cancer therapy should not only stop the proliferation of cancer cells, and kill them but also restore a specific anti-tumor immunity against residual cancer (stem) cells and (micro-) metastases. This requires the induction of immunogenic cancer cell death forms, an increase in tumor antigen presentation, and a decrease in immune regulatory cells.

Cell death can be classified in two extreme forms: apoptosis and necrosis. Apoptosis is a physiologically controlled process, which is normally non-immunogenic or even anti-inflammatory, due to eat-me signals on the dying cells and the subsequent efficient clearance by macrophages. Primary and secondary necrosis, in contrast, both lead to inflammation, because of a

loss of the cellular membrane integrity and the successive release of danger signals or damage-associated molecular patterns (DAMP). These danger signals can be recognized by innate immune cells or dendritic cells (DC) subsequently, which together with antigenic peptides lead to DC maturation and the induction of an innate or adaptive immune response, respectively. Potent danger signals known are for example high-mobility group box 1 protein (HMGB1) and heat-shock proteins like HSP70.

7.2 Immune Functions of HMGB1

The HMGB1 protein is one prominent example of a danger signal being involved in inflammatory conditions. HMGB1 can be actively secreted or passively released during necrosis but not apoptosis, leading to immune activation. In the scope of cancer, extracellular HMGB1 can lead to chronic inflammatory responses that may lead to enhanced tumor cell survival, expansion and metastases. However, a therapy-induced pulsatile release of HMGB1 is capable of inducing specific and long-lasting anti-tumor immunity.
The amount of intracellular HMGB1 was shown to decrease after combined treatment with HT and ionizing irradiation, in comparison to single treatments. Moderate hyperthermia alone is capable of inducing necrotic tumor cell death forms, but only combined treatments (RT plus HT) led to high amounts of immunogenic necrotic cell death forms. We have further shown that combining RT with HT induces the release of HMGB1 by necrotic colorectal tumor cells, a process contributing to anti-tumor immunity.

7.3 Immune Functions of HSP70

HSP70 is a molecular chaperone, present in all cellular and subcellular compartments. It is often overexpressed in tumor cells and could further be found membrane-bound on the surface of tumor cells. Heat-stressed tumor cells release heat-shock proteins, which in turn.

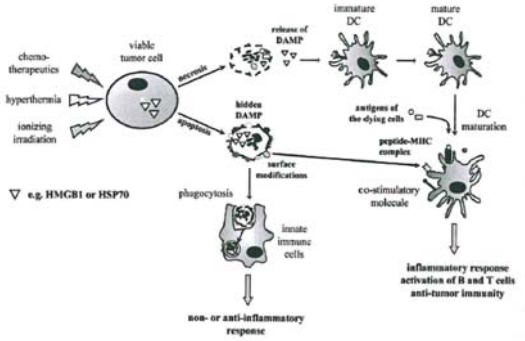


Figure 3. Immune modulation by anti-cancer therapy-induced immunogenic tumor cell death forms

Necrotic cell death forms lead to the release of various DAMP like HMGBl or HSP70. Subsequent recognition by immature DC leads to DC maturation and together with uptake and presentation of peptides of the dying cells to activation of a specific anti-tumor immunity. Apoptotic cells are normally nonimmunogenic, but special surface modifications (like the exposure of calreticulin) also induce immunogenicity.

DC: dendritic cell; DAMP: damage-associated molecular pattern.activate tumor cells to produce chemokines for the attraction of cells of the adaptive immune system, like DC and T-cells. Once in the extracellular space, being e.g. released by necrotic tumor cells, HSP70 gains potent immune stimulatory functions by chaperoning peptides. These HSP70-peptide complexes can instruct DC to cross-present endogenously expressed, non-mutated tumor antigenic peptides. Simultaneously, HSP can also act as free soluble proteins and stimulate the innate immune system by inducing the maturation of DC, the secretion of pro-inflammatory cytokines, and by activating NK cells. Furthermore, HSP exposed membrane-bound on the cell surface render cells more susceptible to

NK cell lysis, which may represent an important cytotoxic mechanism induced by moderate HT treatment. Even hyperthermia in the fever range significantly increases NK cell cytotoxicity against tumor cells, improving the long-term efficacy of clinical HT. Combining HT with immune therapy with DC was also shown to increase the activity of CD8+ T-cells. These properties have made HSP attractive for the development of autologous tumor vaccines that are currently evaluated in clinical trials.

Further known danger signals are uric acid and ATP. Hyperthermia treatment often leads to the depletion of ATP, due to an increased metabolism in the tumor cells. Nevertheless, a reduced cellular ATP level is one initiating step of necrotic cell death, thereby leading to specific immune activation.

Current chemotherapeutics act mostly immunosuppressive, owing to the mainly non-specific cytostatic and cytotoxic effects. However, some anti-cancer agents can induce immune responses, e.g. cyclophosphamide which selectively depletes Tregs and restores normal CD8+ T-cell and NK-cell functions in patients. Kroemer's group could show recently, that some chemotherapeutic agents (mainly anthracyclines) are also able to induce immunogenic forms of apoptosis. Responsible is the very early membrane expression of the endoplasmatic reticulum protein calreticulin, which acts as eat-me signal for DC. Taken together, combinatory treatments (CT, RT and HT) may induce immunogenic necrotic and apoptotic tumor cell death forms finally leading to specific anti-tumor immunity (Figure 3.). HT in combination with standard treatments and HSP-based vaccination, like the autologous transfer of HSP-activated NK cells, may also offer a great potential as a new approach to directly activate the immune system of the patient at the tumor site. Future pre-clinical and clinical studies should focus on immune modulatory effects of HT, to gain more evidence based data supporting that HT in multimodal therapy settings leads to specific anti-tumor immunity.

8. Effectiveness of HT treatment in cancer therapy

Various clinical randomized studies have already proven the effectiveness of an additional hyperthermia treatment, with one or two sessions per week before or after the radiation fraction, for various human cancer entities: cervical, bladder, head & neck, anal canal, esophageal, malignant melanoma, and breast cancer. Clinical endpoints improved include response, local control or disease-free survival of patients without an increase in toxicity or late side effects, which make local or regional HT treatments attractive as radio- or chemosensitizer. Furthermore, a non-randomized clinical trial on bladder cancer revealed promising first results of integrating hyperthermia into the trimodality treatment of transurethral resection and radiochemotherapy (RCT) with enhanced response rates, local control rates, and overall survival.
In patients with poor risk malignancies of the childhood the introduction of HT into standard treatment protocols may be promising to improve tumor response and event-free survival. In addition to the direct interactions of HT with chemotherapy and/or radiotherapy, pharmacological targeted therapies are of great interest. In children and adolescents with unresectable malignant tumors thermochemotherapy resulted in substantial therapeutic efficacy and facilitated complete tumor resection in about 50% of the operated patients.
In general, the outcome of an additional hyperthermia treatment in multimodal therapies is strongly based on the quality of the applied heat treatment. Most of the published randomized data evaluated the effects of local and regional HT combined with RT.

8.1 Rectal Cancer

The Russian randomized trial published by Berdov et al. in 1990 compared RT alone (total dose 40 Gy in 10 fractions of 4 Gy) with RT plus HT treatment. If possible, the tumor was resected

afterwards or another RT (10x 4 Gy) session was applied. The results showed that the complete and partial response rate, 16 vs. 2% and 54 vs. 34%, respectively, were significantly better when RT was combined with HT. The overall survival rate (5 years) was likewise increased (36% vs. 7%) when HT treatment was added to RT. Another study randomized patients (n=l43) with primary or recurrent rectal cancer. The radiation dose was 46-50 Gy in 1.8-2.3 Gy daily fractions, followed if possible by a boost of 10-24 Gy to the tumour mass. Regional hyperthermia was added once weekly with a total of five treatments. No significant differences in complete response and overall survival rates had been found, although there was a trend to better results for the combined arm. Late toxicity was not significantly enhanced by the addition of hyperthermia.

In a German trial, advanced rectal cancer was treated with neoadjuvant RCT or RCT plus deep regional hyperthermia (once a week before radiotherapy), followed by surgery and another CT session. The tumor response with complete and partial response rates could be significantly enhanced by the combined therapy (66% vs. 49%, $P<0.05$). In addition, the time to local recurrence (28 vs. 20 months, $P<0.05$) could be significantly delayed by RHT. Local con-trol could not be significantly improved by the additional hyperthermia treatment. Overall survival probability (3years) was 89% vs. 80% in favor of the HT group, but also not statistic all significant.

In a recent Cochrane review, the existing evidence for the possible beneficial effects of combined HT and RT treatment was summarized. A total of 520 patients from six randomized trials were analyzed. Overall survival after 2 years was significantly better in the hyperthermia group ($P=0.001$) compared to radiotherapy alone, but this difference disappeared after a longer period. A significantly higher pathologically complete remission rate (pCR) was observed in the hyperthermia group ($P=0.01$). However, the authors concluded that further studies are needed in well selected and quality controlled randomized trials.

A multi-institutional phase-II study for locally recurrent rectal cancer (HyRec Trial) is planned, where neoadjuvant chemoradiation with 5-fluorouracil/capecitabine and oxaliplatin and a total dose of 45 Gy will be combined with deep regional HT. Primary endpoints are feasibility rate and number of HT applications by patient.

8.2 Breast Cancer

For primary or recurrent breast cancer, several randomized trials (DHG (NL), MRC (UK), ESHO (EU), PMH (CDN)) were analyzed in a European meta-analysis which compared RT (biologically effective radiation dose between 40 and 70 Gy, with single irradiations from 1.8 to 4 Gy) with RT plus superficial HT. In this study, it was set value on a comparable temperature range (42.5-43 ^{o}C) whereas the number of hyperthermia treatments varied from 2 to 8. The primary endpoint of all trials was local complete response. A total of 306 patients were analyzed: 44% (135/306) received radiotherapy alone, and 56% (171/306) received combined treatment.

Compared to RT alone, RT plus hyperthermia was shown to improve the overall complete remission rate (59% vs. 41%, $P<0.001$) as well as the local control in patients. Despite a significantly enhanced local control, the overall survival was not improved by HT. The clinically relevant acute or long-term toxicity did not increase compared to irradiation alone, even in patients who had received RT before.

Another randomized trial was performed by the Duke University in USA. A total of 108 patients with superficial tumors of different origins were analyzed in detail, treated with radiation alone (n=52) or combined with superficial HT (n=56). Among patients in both arms, the median radiation dose was 41 Gy (range 18 to 66 Gy) if prior radiation was given and the median dose was 60 Gy (range 24 to 70 Gy) if no prior radiation was given. The complete remission rate in the HT arm was 66%, whereas the CR rate in the RT alone arm was only 42% ($P=0.02$). Previously irradiated patients showed the most improvement in local control; 15 of 22 patients in the HT arm (68%) had a complete remission versus 4 of 17 patients in the no-HT arm (24%). The overall survival rate was not found to be significantly different between the two groups.

8.3 Cervical Cancer

For locally advanced cervical cancer, several randomized trials were conducted comparing RT with RT plus HT treatment.

The Dutch Deep Hyperthermia Trial compared RT with combined RHT in 114 women (FIGO stages IIB-IVA). Radiotherapy was applied to a median total dose of 68 Gy and hyperthermia was administered once a week. Primary and secondary end points were local control and overall survival. Local control remained better in the combined group (37% vs. 56%; P=0.01) and in addition, overall survival was better (20% vs. 37%; P=0.03) after 12 years of follow-up. Pelvic-free-failure survival was similarity enhanced when hyperthermia was added, demonstrated by 61 vs. 41%. Late toxicities were not significantly different in both groups. Therefore, this combined treatment should at least be considered for patients who are unfit to receive chemotherapy.
A further randomized trial investigated the impact of hyperthermia in cervical carcinoma patients with FIGO Stage IIIB (n=40). The complete response rate was 80% in the combined group vs. 50% in the radiotherapy group (P=0.048). Overall survival rates (3 years), disease-free survival and relapse-free survival were better in the HT group than those of the patients treated with RT alone. Combined radiotherapy and hyperthermia was well tolerated and did not show significant changes in acute or longterm toxicity.
In 64 patients with cervical cancer (FIGO IIIB), Datta et al. reported on improved complete remission, pelvic control, and overall survival rates in the combined therapy group with radiation and hyperthermia.
In a randomized trial with a total of 50 patients (FIGO stages II-III) Sharma et al. reported on a better pelvic control (70% vs. 50%) in favour of the HT group. A further randomized study compared HT with RT in 120 patients with FIGO IIB-IIIB disease. Combined treatments showed significantly enhanced complete response rates.

8.4 Soft Tissue Sarcoma

For high-risk soft tissue sarcomas, a large phase-III randomized prospective trial compared neoadjuvant chemotherapy with or without additional RHT (EORTC 62961/ESHO RHT95 Intergroup Trial) in order to define the impact of RHT within the treatment strategy for patients with primary or recurrent high-risk soft tissue sarcoma. It was the biggest randomized study ever conducted on hyperthermia treatment, starting in 1997 and finished in 2006.
First results after median follow-up for all patients of 24.9 months (0-106.9 months) showed a significantly enhanced disease-free survival (31.7 vs. 16.2 months) for the patients who received CT (etoposide, ifosfamide anddoxorubicin (adriamycin)) combined with RHT (n=169) compared to treatment with CT alone (n=l72), respectively. Furthermore, tumor response and local progression free survival could also be significantly enhanced by the additional hyperthermia treatment, suggesting that postsurgical HT treatment may be crucial for local control. A further important observation was made that patients seem to improve most from the combined treatment regimen when chemotherapy is given combined with regional hyperthermia after inadequate surgery. A recent update on this phase-III randomized prospective trial after a median follow-up of 34 months could strengthen the previous results: median disease-free survival was 32 vs. 18 months, with an absolute difference at 2 years of 14%. Overall response was more than twice as high, 28.8 vs. 12.7% in favor of the hyperthennia group.

8.5 Further HT Techniques

Besides Regional Hyperthermia other treatment modalities are used in clinical concepts today. Cytoreductive surgery followed by hyperthermia intraperitoneal chemotherapy (HIPEC) was applied in various phase-II studies and one phase-III study (outlined in). One randomized trial for the prevention of peritoneal recurrence of gastric cancer and one multicentre clinical trial

comparing intravesical CT alone with microwave HT for prevention of recurrence in STCC of the bladder showed slight improvements in terms of local recurrence and recurrence-free survival, respectively. However, the HIPEC techniques still remain an experimental approach.
Another important technique is the hyperthermic isolated limb perfusion (ILP). Tumor necrosis factor (TNF) plusmelphalan-based hyperthermic ILP has been proven to be highly effective in multicentre non-randomised trial settings, demonstrating response rates above 70% and limb salvage rates above 80% especially in locally advanced soft tissue sarcomas of the extremities. Similar to the HIPEC techniques, the relative effects of HT combined with TNF and melphalan are still not completely determined.

Conclusion

Taken together, hyperthermia in combination with radiotherapy and chemotherapy can be a useful multifunctional weapon to fight various tumor entities. There is no question of its efficacy in the treatment of cancer patients, provided that the achieved temperature in the tumor tissue is tightly quality controlled. Today, the important question remains for which tumor entity and clinical stage of disease patients are benefiting the most from an additional hyperthermia treatment. The technical improvements of the last ten years led to a quality assured heat delivery in the tumor tissue, even in deep seated malignancies, and therefore dose limiting "hot spots" in normal tissues can be avoided. The mechanisms of HT are complex and its pleiotropic effects are in favor of the combined use with CT and RT in the clinical situation. The current data from randomized phase-III studies clearly indicate the beneficial effects of HT. Future research and clinical trials should prove that in multimodal treatments hyperthermia may induce specific and long-lasting anti-tumor immunity.

Acknowledgements

This work was supported by the ELAN Fond [ST-08.06.30.1] of the Friedrich-Alexander University of Erlangen-Nuremberg, by the European Commissions [NOTE (TPA4 FP6)], and by the German Research Foundation [Graduate school of the SFB 643]. We further thank the members of the Scientific Study Group for Hyperthermia in Radiooncology and Clinical Oncology "Atzelsberger Kreis" for the fruitful discussions about the application and technique of temperature-controlled hyperthermia.

Abbreviations

ATP = Adenosintriphosphate
CT = Chemotherapy
DAMP = Damage-associated molecular pattern
DC = Dendritic cell
DSB= Double-strand break
HIPEC = Hyperthermic intraperitoneal chemotherapy
HSP =heat-shock protein
ILP = Isolated limb perfusion
HT = Hyperthermia
NK cell =Natural killer cell
RCT= Radiochemotherapy
RHT = Regional hyperthermia
RT = Radiotherapy
TER = Thermal enhancement ratio

Oncothermia Journal 10:147-154 (2014)

Radiation combined with hyperthermia induces HSP70-dependent maturation of dendritic cells and release of pro-inflammatory cytokines by dendritic cells and macrophages

Petra Schildkopf[1], Benjamin Frey[1], Oliver J. Ott[1], Yvonne Ruvner[1], Gabruele Multhoff[2], Rolf Sauer[1], Rainer Fietkau[1], Udo S. Gaipl[1]

(1) Department of Radiation Oncology, Radiation Immunobiology, University Hospital Erlangen
(2) Friedrich-Alexander University of Erlangen-Nürnberg, Universitasstr. 27, 91054 Erlangen, Germany

Radiation combined with hyperthermia induces HSP70-dependent maturation of dendritic cells and release of pro-inflammatory cytokines by dendritic cells and macrophages

Abstract

Purpose

Hyperthermia (HT) treatment of cancer patients was revived over the last years and has been proven to be beneficiary for many cancer entities when applied temperature controlled in multimodal treatments. We examined whether a combination of ionizing irradiation (X-ray) and HT (41.5 C; 1h) can induce the release of heat shock protein (HSP) 70 by tumor cells and thereby lead to the activation of dendritic cells and macrophages.

Material and methods

Extracellular HSP70 was detected in supernatans (SN) of treated colorectal tumor cells by ELISA. Maturation of dendritic cells (DC) after contract with the SN was measured by flow-cytometry. Phagocytosis assays were conducted to get hints about the immune stimulating potential of the tumor cells after the respective treatments.

Results

An increased surface expression of HSP70 was observed after X-ray or X-ray plus HT while the amount of extracellular HSP70 was only increased when HT was given additionally. A high up-regulation of the co-stimulation molecule CD80 and the chemokine receptor CCR7 on DC was measured after contact with SN of X-ray plus HT treated cells. This was dependent on extracellular HSP70. Combined treatments further led to significantly increased phagocytosis rates of macrophages and DC and increased proinflammatory cytokine (IL-8 and IL-12) secretion.

Conclusion

X-ray combined with HT induces HSP70 dependent activation of immune cells and might generate a tumor microenvironment beneficial for cure.

Keywords

Radiotherapy, Hyperthermia, Heat-shock protein 70, Dendritic cells, Macrophages, Immune activation

As a single treatment, hyperthermia (HT) is not capable to replace established standard cancer treatments like radiotherapy (RT) with X-ray and treatment with chemotherapeutics. However, several experiments and studies proved that HT induces thermal chemo- and radio-sensitization. Various clinical randomized trials have already shown the effectiveness of an additional HT treatment for the disease-free survival of patients and local tumor control for various human cancer entities, without an increase in toxicity. Also in palliative settings and recurrent cancer, HT was shown to prolong local progression free survival when combined with radiochemotherapy. Most of the pre-clinical mechanistic studies on the mode of action of HT focused on the in vitro clonogenic potential of tumor cells after RT in comparison to RT plus HT. However, only few data exist dealing with the immune modulatory effect of locally applied HT when added to RT.

Heat shock proteins (HSP) are prominent proteins induced by HT treatment. Besides constitutively expressed HSP inducible forms exist, which help to protect the cell against damage after a variety of different stress stimuli like heat, oxidative stress, cytotoxic agents or radiation. Tumor cells often show up-regulated intracellular basal levels of inducible HSP. In addition, HSP70 was reported to be secreted by tumor cells and elevated sera levels were observed in cancer patients,

like HSP72 after X-ray. Extracellular HSP may act as immune activating danger signals and stimulate innate as well as adaptive immune responses. Extracellular HSP70 can bind to receptors on professional antigen presenting cells (APC) and initiate the release of pro-inflammatory cytokines and the maturation process.

Dendritic cells (DC) are potent APC. Immature DC (iDC) migrate throughout the body and take up various antigens (Ag) efficiently, but presentation of these Ag on MHC molecules is initially weak. DC must undergo a maturation process, initiated by e.g. inflammatory cytokines. Maturation is characterized by an increase in surface markers responsible for co-stimulation. The uptake of further Ag by DC is reduced during this process, which results in a decrease of the C-type lectin receptor CD209 (DC-SIGN). Furthermore, homing-receptors like CCR7 show increased expression, and different pro-inflammatory cytokines and chemokines are secreted by the mature DC. The latter migrate subsequently to draining lymph nodes, where they are able to prime antigen-specific CD8 +cytotoxic T-cells (CTL).

Tumor associated Ag can be chaperoned by HSP70, taken up and cross-presented on MHC I molecules by DC. We already demonstrated that mild HT in addition to X-ray fosters necrotic cell death and release of the danger signal HMGB1 of colorectal tumor cells. The rationale of the present study was to get preclinical immune biological mechanistic insights how temperature controlled HT (at least 41 ^{o}C for at least 1 h), when added to RT, may contribute to improved tumor control in cancer patients. In addition, the importance of the immune system in cancer therapies is long proven, but the molecular mechanisms of HT on the immune system are still elusive. Therefore, we examined how X-ray and HT influence the secretion of HSP70 by colorectal tumor cells and the subsequent activation of cells of the adaptive (DC) as well as innate (macrophages) immune system.

Materials and methods

Cell culture

Human colorectal tumor cell lines (HCT15 and SW480) and mouse colon carcinoma tumor cell line CT26.WT (CRL-2638) were used for the analyses. The cell lines were tested negative for myco-plasma with per detection kit (Minerva Biolabs, Germany).

X-ray and HT treatment of the tumor cells

Cells were irradiated with different doses (2, 5 and 10 Gy) of X-ray (120 kV, 22.7 rnA, variable time; GE Inspection Technologies, Germany). For HT, cells were treated with 41.5 ^{o}C for 1 h as described previously. The temperature variations which the tumor cells were exposed to were less than 0.2 C. Therefore, a constant and temperature stable heat delivery to the cells was assured.

Analysis of the danger signal HSP70

The quantification of HSP70 supernatantis (SN) was performed with an enzyme-linked-immunosorbent assay (ELISA) DuoSet IC Kit (R&D Systems) according to the manufacturer's instructions. The remaining cells were used for flow cytometric analysis (GalliosTM, Beckmann Coulter) of membrane-bound HSP70 with FITC-labeled anti-HSP70 cmHsp70.1 antibody (multimune, Munich, Germany).

Isolation of PBMC and generation of iDC

Human peripheral blood mononuclear cells (PBMC) were generated from heparinized whole blood samples from healthy human donors by ficoll (Biotest, Germany) density gradient separation. PBMC were sown in 6-well plates (Greiner BioOne, Germany). After 1.5 h incubation at 37 ^{o}C, non-adherent lymphocytes were removed by washing. To generate iDC, adherent monocytes were cultured for 6 days in RPMI 1640 medium (Gibco, Germany) supplemented with 10% FBS (Biochrom AG, Germany), 1% L-glutamine, 1% sodium pyruvate and 1% penicillin-streptomycin (all from Gibco, Germany) plus the appropriate differentiation cytokines: 250 U/ml IL-4 (Immuno

Tools, Germany) and 800 U/mlGM-CSF (Leukine sargramostim; Bayer Schering AG, Germany). Fresh medium was added on day 2 and 5 of culture, containing.

Flow cytometric analyses of DC activation

Activation of iDC was induced over night on day 6 with undiluted tumor cell culture SN. Afterward, DC were detached and stained for activation markers. The following fluorochrome conjugated antibodies were used: CD14-FITC and HLA-DR-Pacific blue (both Beckman Coulter), CD19-FITC, CD83-PE, and CCR7-PC7 (all from BD Pharmingen), CD80-PC7, CD86-PerCP/Cy5.5, CD25-Pacific blue, and CD40-PerCP/Cy5.5 (all from Biolegend), and DC-SIGN-APC (eBioscience). For blocking experiments, anti-HSP70 (BD Bio-sciences, USA) or anti-HMGB1 (Upstate, USA) antibody (both1:1000) was added to cell culture SN and pre-incubated for 15 min before adding the SN to the DC.

Generation of macrophages and phagocytosis assays

Human PBMC were stained red with Vibrant Dil (Invitrogen, Germany). Afterward, cells were washed and sown in 48-well plates (Greiner BioOne, Germany). After 1.5 h incubation at 37°C, nonadherent lymphocytes were removed by washing and adherent monocytes were cultured for 6 days in RPMI medium supplemented with 20 % autologous serum and 1 % penicillin-streptomycin (Gibco, Germany), to generate human monocyte-derived macrophages (MU).

On day 5 or 6, DC and MU were activated with 500 ng/ml pure LPS (Sigma, Germany), respectively, for the detection of cytokines. For phagocytosis assays, the red (Dil) stained human monocyte derived macrophages were co-incubated with the green (CFSE) stained prey. Shortly, the CFSE-labeled tumor cells were treated with RT and/or HT as described above, cultured for 24 h and then added in a five fold increased amount to the Dil stained macrophages. After 1 h of co-incubation at 37°C, the SN was removed, collected, and stored at 80^{o}C for further analysis of secreted cytokines, and the macrophages were detached from the wells for analyses by two-color flow cytometry. The double positive cells (Dil and CFSE) detected by flow cytometry are macrophages that have phagocytosed the tumor cells. To exclude a simple adhesion of the prey to the surface of the macrophages, confocal microscopic control analyses were performed. This kind of phagocytosis assay is used in many studies and was established and published by our group before. For phagocytosis of CSFE-stained and treated tumor cells by DC, the same assay was performed using Dil stained monocyte derived dendritic cells as phagocytes.

Analysis of secreted cytokines from activated macrophages and DC

SN from macrophages and DC were analyzed for cytokines by standard ELISA. The appropriate kits (TGF-b (R&D Systems), TNF-a, IL-10, IL-12p70 and IL-8 (ELISA Max Sets, all from Biolegend, San Diego, USA)) were used according to the manufacturers' instructions.

Mice experiments

The animal studies were conducted according to the principles in the guidelines for the care and use of laboratory animals and were approved by the "Regierung von Mittelfranken". For the syngeneic clonogenic in vivo experiment, female Balb/c mice (Charles River Laboratories, Sulzfeld, Germany) were injected subcutaneously with 4x10^{6} CT26 RT and/or HT treated tumor cells suspended in Ringer's solution (DeltaSelect, Germany) into the flank. Tumor outgrowth was then monitored at day 3, 10, and 14 after the injection of the tumor cells. At day 14 we stopped the analyses, since mice that have received untreated tumor cells had to be euthanized because of the large size of their tumors.

To get first in vivo hints about the immunogenicity of X-ray and/or HT-treated human HCT15 tumor cells, female Balb/c mice at an age of 4-6 weeks were immunized three times every 14 days i.p. with 4x10^{6} human viable or treated HCT15 cells. Viable human HCT15 cells, being a xenogeneic material for mice, always lead to a high immune response in mice. To compare the

effect of the treatments on the immunogenicity of the tumor cells, the increase or decrease of the specific immune response against treated HCT15 cells in comparison to viable ones was determined. For analysis of tumor cell-specific antibodies in the sera of mice, blood samples were taken before and after each immunization and analyzed by indirect immune fluorescence. Briefly, viable HCT15 target cells were incubated with the serum of the immunized mouse for 60 min at 4°C in the dark. Afterward, cells were washed and bound antibodies were analyzed by flow cytometry using a FITC-tagged F(ab')2 fragment of goat anti-mouse IgG (Invitrogen, Molecular Probes, Germany). Unspecific binding of lgG antibodies was accounted by subtraction of the values of the binding of control lgG from those obtained with serum of the immunized mice.

Statistical analyses

Statistical analyses of ELISA and flow cytometric data were performed using the unpaired Student's test. For analyses of the in vivo mouse data, the Mann-Whitney-U Test was applied in addition.

Results

X-radiation alone and in combination with HT leads to an increased exposure of HSP70 on the outer tumor cell membrane

We detected a significantly increased exposure of HSP70 on the surface of HCT15 colorectal tumor cells after X-ray or X-ray plus HT (Figure 1A). Using X-ray in combination with HT, the amount of membrane-exposed HSP70 protein was significantly decreased in comparison to irradiation only, both at an early (24 h) and late time point (not shown) after treatment. We hypothesized that the induced form of HSP70 may be released at higher rates into the extracellular space by tumor cells after an additive HT treatment.

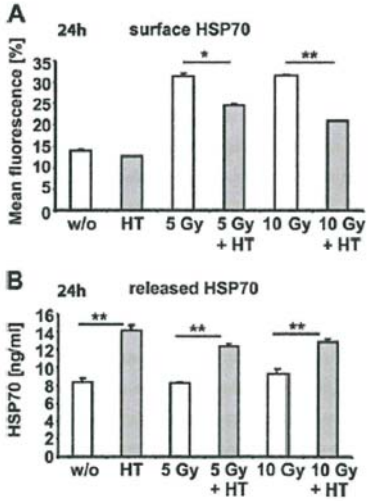


Figure 2. Membrane-exposed and extracellular HSP70 after X-ray and/or HT. Human colorectal tumor cells were treated with X-ray and/or HT. The amount of membrane-exposed HSP70 24 h after the respective treatments was detected by flow cytometry (A), and extracellular HSP70 was detected by ELISA. (B) Representative data from 1 out of 3 independent experiments, each performed in duplicates, are displayed; P < 0.05,//P < 0.01. HT: hyperthermia; w/o: mock treated control

Combinations of HT with X-radiation lead to an increased release of HSP70

We detected a significantly increased amount of extracellular HSP70 protein after HT treatment alone (Figure 1B). X-ray alone did not significantly affect the extracellular amount of HSP70. The combined treatment increased the amount of extracellular HSP70 significantly, with 2 Gy (not shown), 5 Gy, or higher (10 Gy) radiation doses (Figure 1B). At later time points, the effect of the

combinatory treatment is similar, although higher amounts of total extracellular HSP70 are achieved (not shown).

Supernatants of X-radiation plus HT treated tumor cells induce maturation of DC

Human iDC were cultured with tumor cell culture SN. The maturation marker CD83 was only slightly up-regulated on DC by all cell culture supernatants. However, the expression of CD83 was not influenced by the different cell-death initiators used (Figure 2A). Similar results were obtained for other maturation markers like CD40 (Figure 2C), HLA-DR (Figure 2D), and CD86 (Figure 2E). In contrast, CD209 was down-regulated after contact of DC with supernatants of the tumor cells (Figure 2F). The co-stimulation marker CD80 was only slightly up-regulated by the SN of X-radiation treated cells, whereas SN of HT, or most prominently SN of X-ray plus HT treated cells, significantly increased the expression of CD80 on DC (Figure 3A). The expression of the chemokine receptor CCR7 was also significantly increased after contact of DC with SN of X-ray plus HT treated cells (Figure 3B). Blocking experiments revealed that inducible HSP70 (Figure 3C), and not HMGB1 (Figure 3D), was responsible for the upregulation of CD80 as well as CCR7.

Supernatants of X-radiation plus HT treated tumor cells foster phagocytosis of tumor cells by macrophages and increase IL-8 secretion

We were interested in how X-ray and hyperthermia treatment of tumor cells influence their phagocytosis by macrophages. MU showed slightly diminished phagocytosis of tumor cells treated with X-radiation only, although the difference to untreated tumor cells was not significant. In contrast, hyperthermia treatment alone, and more pronounced in combination with X-radiation, significantly enhanced phagocytosis of tumor cells by MU (Figure 4A), which positively correlated with the radiation dose. Regarding the cytokine secretion by MU during phagocytosis, only low amounts of anti-inflammatory cytokines like IL-10 and TGF-b (not shown) were detected, while X-radiation plus HT significantly restored the secretion of the inflammatory cytokine IL-8 (Figure 4B). Another pro-inflammatory cytokine, TNF-a, was secreted in only moderate amounts and no difference between the distinct treatments was observed (not shown).

Supernatants of X-radiation plus HT treated tumor cells foster phagocytosis of tumor cells by DC and increase IL-12 secretion

DC displayed similar phagocytic activity as MU, although HT alone did not significantly increase the uptake of tumor cells by DC (Figure 4C). Combinations of X-ray with HT again increased the phagocytic activity of DC, highly significant. Activated DC secreted low amounts of IL-12p70 during phagocytosis of untreated, HT, or 2 Gy treated tumor cells (Figure 4). However, 2 Gy plus HT significantly increased the amount of secreted IL-12p70 to a similar extent as treatment with 5 Gy, 5 Gy/HT, 10 Gy, or 10 Gy/HT (Figure 4D).

Discussion

Besides targeted effects of ionizing irradiation on cellular DNA, abscopal effects arise after X-ray that may contribute to the development of anti-tumor immunity. Targeting the tumor locally by RT is capable to induce systemic effects by modulating the immune system. One main stimulus comes from the form of therapy-induced tumor cell death and the concomitant release of immune activating danger signals. In the future, immunological parameters may add value for predictive models for complete response of rectal cancer patients.

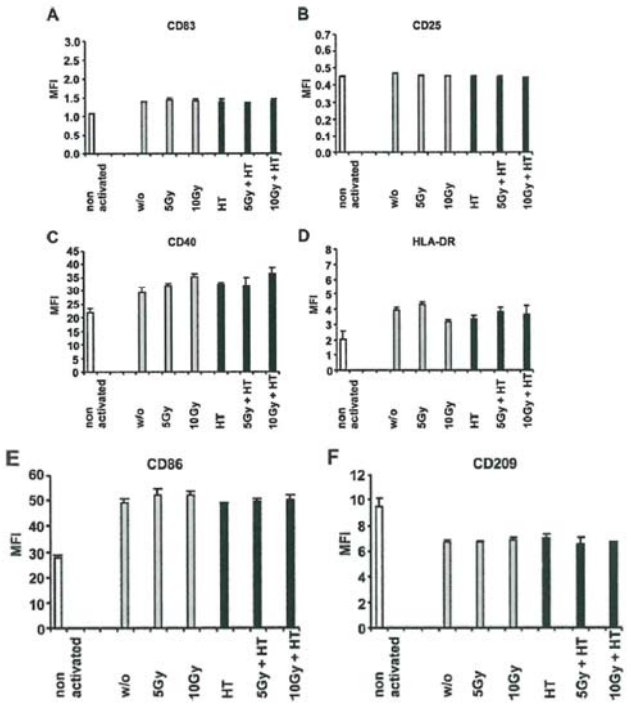


Figure 2. Maturation and co-stimulatory markers of DC after contact with SN of X-ray and/or HT treated tumor cells. Human DC were co-incubated with SN of X-ray/HT treated colorectal tumor cells. Maturation markers were detected using flow cytometry. The data are obtained from 1 out of 3 independent experiments, each performed in duplicates

Already elegantly established for imaging methods. Most of the pre-clinical assays performed focused on the in vitro clonogenic potential of tumor cells after RT in comparison to RT plus HT. We conducted in addition to the above presented results a syngeneic in vivo clonogenic assay with colorectal CT26 tumor cells in Balb/c mice. Cells treated with HT alone displayed a slightly faster tumor growth in comparison to untreated cells, indicating that HT only treatment may.

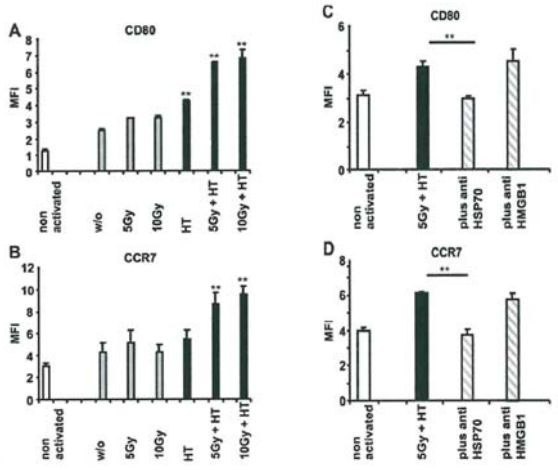


Figure 3. The role of HSP70 in up-regulation of CD80 and CCR7 on DC after contact with SN of X-ray and/or HT treated tumor cells. Human DC was co-incubated with SN of X-ray/HT treated colorectal tumor cells. CD80 (A) and CCR7 (B) expressions were detected 24 h after treatment using flow cytometry. The up-regulation of CD80 (C) and CCR7 (D) expressions was dependent on HSP70. The data are obtained from 1 out of 3 independent experiments, each performed in duplicates.//$P < 0.01$

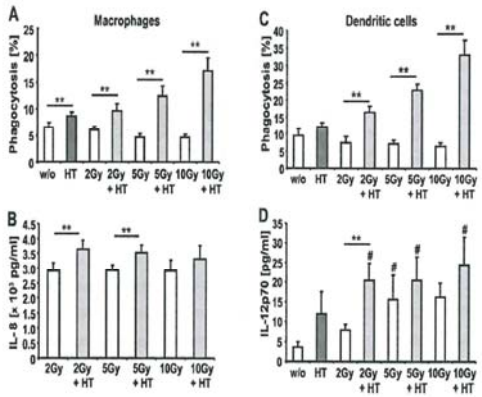


Figure 4. Phagocytosis of X-ray and/or HT treated tumor cells and cytokine secretion by macrophages and DC. Phagocytosis of colorectal tumor cells by macrophages (A) and DC (C) was measured by flow cytometry. Cytokines were detected in SN of macrophages (B) and DC (D) using ELISA technique. Representative data from one out of two independent experiments, each performed in independent pentaplicates, are displayed.//P <0.01. #P < 0.05 (against w/o)

Even foster in vivo tumor outgrowth. A significant tumor growth retardation was observed, as expected, when the tumor cells were irradiated with 5 or 10 Gy. However, a single irradiation with 2 Gy did not significantly retard the tumor outgrowth in vivo, while a combination of 2 Gy with HT was as effective as 5 Gy or 5 Gy plus HT (Supplementary Figure 1), indicating that HT added to RT has beneficial effects on tumor growth retardation. However, besides those data on clonogenic potential of tumor cells (targeted effects) only few data exist dealing with the systemic, immune sensitizing effects of HT when added to RT. HT is capable to foster programed.

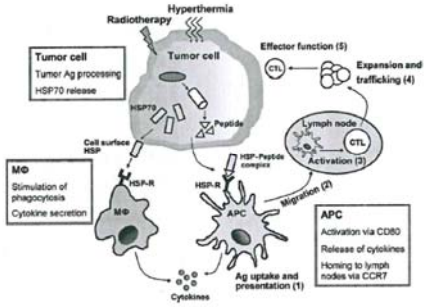


Figure 5. HT plus X-ray lead to HSP70 dependent immune activation. Inside a tumor cell, various tumor-antigens are processed into peptides, chaperoned by heat-shock protein 70 (HSP70) and secreted into the tumor microenvironment. Here, they can interact with antigen presenting cells (APC) like DC, which leads to activation, Ag uptake and presentation (1). Subsequently, after migration (2) to lymph nodes, tumor-specific CD8 + T-cells can be induced (3). After their expansion and trafficking back to the tumor (4), the T cells exert their effector function as CD8 + cytotoxic T lymphocytes (CTL; 5). In addition, HSP can directly activate macrophages, which leads to enhanced phagocytosis of tumor cells and secretion of pro-inflammatory cytokines. Modified accordingly.

Cell death pathways like necroptosis that may mediate radio-sensitizing effects. The latter were just recently discovered to be also triggered by autophagy as cell death pathway. We hypothesized in the present study that RT plus HT leads to immune activation by inducing the release of the inducible form of HSP70 from colorectal tumor cells and were further interested in its impact on DC and macrophages. We confirmed an increased surface expression of HSP70 after X-ray treatment of tumor cells. However, only HT alone or the combination of HT with X-ray led to significantly increased amounts of secreted HSP70. Secreted danger signals are mandatory as co-stimulatory molecules for the induction of an adaptive immune response. Dendritic cells present antigens (Ag) to CD4+ and CD8 + T cells. Because of its well-known function of chaperoning tumor Ag to professional APC, we analyzed the impact of an increased HSP70 release by colorectal tumor cells on the maturation of human DC. SN of X-ray and/or HT treated colorectal tumor cells led to up-regulation of several DC markers involved in maturation and co-stimulation (HLA-DR, CD40, and CD86). The co-stimulation marker CD80 and the chemokine receptor

CCR7 were only significantly enhanced on DC after contact with SN of tumor cells treated with X-ray plus HT. CD80 is the prominent co-stimulation marker of DC and up-regulation of CCR7 receptor is a prerequisite for migration of DC to lymph nodes. There, DC cross-present the chaperoned tumor Ag, activate CTL and can thereby induce specific anti-tumor immunity. We showed that DC and macrophages take up colorectal tumor cells better when they have been treated with X-ray plus HT instead of X-ray alone (Figure 4). Increased phagocytosis of tumor cells by DC subsequently can lead to increased presentation of tumor Ag.

Pro-inflammatory cytokines might result in autocrine activation of immune cells or activation of further cell types, such as natural-killer cells and T-cells. Furthermore, macrophages, like DC, are able to induce anti-tumor immunity by production of Th1 cytokines leading to subsequent stimulation of CTL. We identified that macrophages and DC secrete pro-inflammatory cytokines such as IL-8 and IL-12 after phagocytosis of X-ray plus HT treated tumor cells. The secretion of anti-inflammatory cytokines like TGF-b was low. TGF-b secretion is predominantly observed after X-radiation with low (single dose 6 0.1 Gy) and intermediate dose (single dose 61.0 Gy). It is one main player in exerting the anti-inflammatory effects of low dose X-ray. At higher single dose (> 1.0 Gy) only low amounts of TGF-b are normally observed.

Chen and colleagues recently demonstrated in an in vivo mouse model that superficial hyperthermia treatment induced the maturation of DC and suggested that the release of HSP70 is essential for this. We conclude from data presented in this manuscript that the addition of HT to the conventional treatment with X–ray retards in vivo tumor outgrowth and might increase the immune activatory potential of tumor cells, or at least maintain the one induced by X-ray, via activation of DC and stimulation of inflammatory cytokine secretion by DC and macrophages. Fig. 5 summarizes how X-ray and HT may lead to specific activation of the immune system via the induced release of HSP70.

Future research should focus on the in vivo immunogenicity of RT and/or HT treated tumor cells. We performed a first xenogeneic in vivo assay according Stach et al. testing whether treatment with RT plus HT increases the immunogenicity of human HCT15 cells in Balb/c mice. The amount of tumor-cell specific IgG antibodies did not differ significantly between untreated and HT only treated human tumor cells. Of note, cells treated with a clinically relevant single dose of 2 Gy do not show increased lgG antibody levels, but the addition of HT leads to a significant increase in tumor-specific IgG antibodies (Supplementary Figure 2). Higher dose of RT (e.g. 5 Gy) alone is capable to maintain the immunogenicity of tumor cells, clearly showing that RT treatments alone or in combination with HT do not reduce the immunogenicity of tumor cells, as e.g. described for apoptotic tumor cells that have been killed with UV irradiation. Besides exerting a general and timely restricted immune suppression, X-ray alone and in combination with HT is also capable to induce an immune activatory tumor microenvironment (Figs. 1, 3, and 4) and does not reduce the immunogenicity of tumor cells (Supplementary Figure 2).

Acknowledgments

This work was supported by the German Research Foundation (GA 1507/1-1), the German Federal Ministry of Education and Research (BMBF, m4 Cluster, 01EX1021R), and the European Commissions (NOTE-Integrated Project, TPA4 FP6, contract number 036465). We thank Dr. Niels Schaft and Dr. Jan Dörrie from the Department of Dermatology of the University Hospital Erlangen for their excellent advice about dendritic cell maturation and activation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2011.05.056.

Oncothermia Journal 10:155-155 (2014)

Influence of Moxibustion effects on Immune Function in patients diagnosed with cancer

Chang-Lin Zhao[1]
(1) Clifford University of Guangzhou Chinese Medicine

Abstract
This paper summarize the influence of Moxibustion effects on Immune Function in patients diagnosed with cancer.

Keywords
Moxibustion, cancer, immunity

Oncothermia Journal 10:156-156 (2014)

Research of nursing care in Hyperthermal Perfusion Chemotherapy on Bladder cancer

Chang-lin Zhao, Jun-hua Wang[1]

(1) Oncology Department, Clifford Hospital of Guangzhou University of Traditional Chinese Medicine, China Guangzhou 511495

Objective

To explore the nursing care method in endogenous bladder treating with Hyperthermal Perfusion Chemotharpy.

Method

Line method in bladder cancer peritoneal perfusion chemotherapy, chemotherapy drugs in the bladder give students field of hyperthermia.

Results

100% cure rate, 220 bladder perfusion chemotherapy the incidence of chemical cystitis 3.7%, mainly due to high concentrations of chemotherapy drugs.

Conclusion

The field of bladder cancer perfusion endogenous high chemotherapy, the improvement of nursing measures can effectively improve the efficacy and reduce complications.

Keywords

Bladder cancer, Hyperthermal Perfusion Chemotherapy, Nursing

Oncothermia Journal 10:157-157 (2014)

Clinical Application of Ion Radiofrequency Deep Regional Hyperthermia in Senile Knee Osteoarthritis

Yanhui Tang[1], Junhua Wang[1], Yalin He[1], Jie Liu[1]

(1) Hyperthermia Center, Clifford University of Guangzhou University of Chinese Medicine, Guangzhou, China 511495

Objective

To investigate the treatment efficacy of deep hyperthermia for senile knee osteoarthritis.

Methods

60 cases of senile knee osteoarthritis patients were randomly divided into treatment group and control group. Treatment group: received radiofrequency deep hyperthermia treatment for 30 times. Control group: routinely received oral Non-Steroidal Anti-Inflammatory Drug -Ibuprofen capsules and Calcium Carbonate and Vitamin D3 for 30 days. Analgesic efficacy was observed, and joint function was evaluated.

Results

All patients treated were followed up for 3 months, the total effective rate of the treatment group was 96.7% and the control group, 70%, the total treatment efficacy of the treatment group was significantly higher than the control group, the difference was statistically significant($P < 0.05$).

Conclusions

The radiofrequency deep regional hyperthermia is a simple, noninvasive, safe, non-toxic and effective treatment method for treating senile knee osteoarthritis, it can improve the life quality for the elderly patients and is worthy further promotion.

Keywords

Radiofrequency deep hyperthermia; Elderly; Knee osteoarthritis

Oncothermia Journal 10:158-158 (2014)

Extracorporeal RF Deep Hyperthermia in Combination with Traditional Chinese Medicine on Haemorrheological and Blood Stasis Type Primary Dysmenorrhea

Chen Jianhong[1], Zhang Jianfeng[1], Li Yuling[1], Huang Shu-ai[1], Wei Kaiyi[1], He Yalin[1], Shi Yiaojuan[1], Lu Yimin[1]

(1) Hyperthermia Centre, Clifford Hospital, Guangzhou 511495, China

Purpose

To discuss the efficacies of extracorporeal RF deep hyperthermia in combination with traditional Chinese medicine treatment for haemorrheological and blood stasis type primary dysmenorrhea.

Method

130 cases of patients with dysmenorrhea have been divided into the treatment group and control group, 65 cases for each group. Treatment group: take traditional Chinese medicine Wenjing Soup orally plus extracorporeal RF deep hyperthermia; control group: only take traditional Chinese medicine Wenjing Soup orally.

Result

Among the 60 cases of the treatment group who have finished the observation, 27 cases have obvious efficacies, 26 cases have efficacies, 7 cases have no efficacy and the effective rate is 83.33% (53/60); and among the 56 cases of the control group who have finished the observation, 13 cases have obvious efficacies, 28 cases have efficacies, 15 cases have no efficacy and the effective rate is 73.21% (41/56); through data analysis, the difference is statistically significant ($X2=4.31$, $P<0.05$).

Conclusion

For the treatment of haemorrheological and blood stasis type primary dysmenorrhea, extracorporeal RF deep hyperthermia combination of traditional Chinese medicine has better efficacies than single traditional Chinese medicine treatment.

Keywords

Primary dysmenorrhea, RF deep hyperthermia, haemorrheological and blood stasis type, Wenjing Soup

Oncothermia Journal 10:159-159 (2014)

The clinical observation of the biological electromagnetic pulse therapy on improving the quality of life of cancer patients

Zhang Jianfeng[1], Li Yuling[1], Huang Shu-ai[1], Wei Kaiyi[1], He Yalin[1]

(1) Hyperthermia Centre, Clifford Hospital, Guangzhou 511495, China

Purpose

To observe the biological electromagnetic pulse therapy for improving the quality of life of patients with cancer.

Method

Apply biological electromagnetic pulse therapy on 108 cases of patients with cancer, one time per every 2 days, 10 times as one course of treatment. Conduct comparison before and after the treatment with the QOL rating sheet for patients with cancer.

Effect

After a course of biological electromagnetic pulse therapy treatment, the scores on the mind, sleeping, fatigue and pain etc. of patients with cancer have been improved. The score difference before and after the treatment is statistically significant ($p<0.05$). While the two items, sleeping and pain, have obvious statistical differences ($p<0.0l$). In summary, the total scores of quality of life for patients with cancer before and after the treatment also have obvious statistical differences ($p<0.01$). And all the patients are with no treatment adverse reaction.

Conclusion

The biological electromagnetic pulse therapy can improve the symptoms such as sleeping, pain, spirit, fatigue etc. of patients with cancer which will obviously improve the quality of life of patients with cancer and is worthy of promotion.

Keywords

Biological electromagnetic pulse therapy, cancer, quality of life

Oncothermia Journal 10:160-160 (2014)

Suppression of Human Cancer Cell Growth In Vitro by Oncothermia

Hee-Bum Yang[1], Miyoung Shin[1], Yun-Han Lee[1], Chang-Geol Lee[1]
(1) Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, Korea

Purpose
In the present study, we investigated the potential of oncothermia (electro-hyperthermia) for an alternative therapeutic option of pan-human cancer.

Materials and methods
To address this issue, we applied oncothermic heating (42^{o}C 1 hour, three times with a two- or three-day interval) to various human cancer cell lines such as A549 (lung cancer), HepG2 (liver cancer), MDA-MB231 (breast cancer) and A172 & U-87MG (brain cancer), and then examined for cancer cell phenotypic changes. Cell growth was analyzed by an MTT assay or microscopic observation in 3 days of the third oncothermic heating, and apoptosis was estimated in 24 h of the third treatment by ELISA for the detection of denatured ssDNA only formed during apoptotic progression. In addition, the changes in apoptotic cell population was assessed by flow cytometry. The expression of heat shock protein 70 (HSP70), which is known for a typical marker of heat resistance, was determined by quantitative real-time PCR.

Results
As results, oncothermia effectively inhibited the growth of A549, HepG2, MDA-MB231, A172 and U-87MG cells by about 45%, 70%, 47%, 44% and 75%, respectively, accompanying with remarkable morphological changes in cellular level. We also proved that inhibition of U-87MG cell growth was due to increased rate of apoptotic cell death which was about 2-fold higher than in unheated control cells. FACS analysis showed that oncothermic heating (three times with a three-day interval) to U-87MG and A172 glioma cells retards cell cycle progression and increases the apoptotic cell population by about 17% and 7%, respectively. Meanwhile, we observed that the treatment conditions of oncothermia still upregulate the expression of HSP70 by about 84-fold higher in both U-87MG and A172 cells, in 24 h of the third treatment. It may imply that multiple heating could overcome heat-resistance to drive therapeutic outcome in terms of cancer phenotypic changes.

Conclusion
Taken together, these results indicate that oncothermia maybe an attractive alternative for pan-cancer treatment. Further studies should be warranted to investigate the molecular mechanisms underlying the cancer phenotypic changes induced by oncothermia.

Keywords
Oncothermia, lung cancer, liver cancer, breast cancer, brain cancer, growth inhibition, apoptosis, molecular mechanism

Hindawi Publishing Corporation

Conference Papers in Medicine

We are only presenting you the first page of every article. If you are interested in the full text, please contact us (leckler@oncotherm.de)

Conference of the International Clinical Hyperthermia Society 2012

Gianfranco Baronzio[1], Michael Jackson[2], Dooyun Lee[3], and András Szász[4]
(1) Centro Medico Demetra, Center for Clinical Hyperthermia and Immunity, 05100 Terni, Italy
(2) Prince of Wales Hospital, Sydney, NSW2031, Australia
(3) Gangnam Severance Hospital, Yonsei University, Seoul 135-720, Republic of Korea
(4) Biotechnics Department, St. Istvan University, Godollo 2100, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 690739, 3 pages
http://dx.doi.org/10.1155/2013/690739

Editorial

Conference of the International Clinical Hyperthermia Society 2012

Gianfranco Baronzio,[1] Michael Jackson,[2] Dooyun Lee,[3] and András Szász[4]

[1] *Centro Medico Demetra, Center for Clinical Hyperthermia and Immunity, 05100 Terni, Italy*
[2] *Prince of Wales Hospital, Sydney, NSW 2031, Australia*
[3] *Gangnam Severance Hospital, Yonsei University, Seoul 135-720, Republic of Korea*
[4] *Biotechnics Department, St. Istvan University, Godollo 2100, Hungary*

Correspondence should be addressed to András Szász; szasz.andras@gek.szie.hu

Received 4 November 2013; Accepted 4 November 2013

Cancer has been a permanent fear for human kind since the ancient era. Since the ancient times, we have continuously fought against malignant disease, and this has been one of the greatest challenges in medical science for centuries. In 1971, "war" was declared in the United States against cancer. Oncology has now become one of the most interdisciplinary research fields and includes biology, biophysics, biochemistry, genetics, environmental sciences, epidemiology, immunology, microbiology, pathology, physiology, pharmacology, psychology, and virology. Moreover, a wide range of diagnostic and treatment methods are available to identify and destroy malignant tissue. Enormous economic and human resources are involved in this field, but we have only been partially successful. According to epidemiological data, the complete solution is still much awaited.

The 31st Annual Conference of the International Clinical Hyperthermia Society (ICHS) was a part of the "war." The topic is not new, hyperthermia is an ancient treatment, which is in fact the very first used in oncology. After a long dormant period, hyperthermia has been renewed, with the delivery of electromagnetic energy giving new perspectives. Definitely, hyperthermia promises a lot; a method with low toxicity and rare complications is a long-time dream and at the same time is one of the great needs of oncology practice. The combination of biochemical approaches with biophysical methods could be a perfect combination giving a synergistic destruction of malignancy. Oncological hyperthermia is an ideal combination therapy; it provides synergies with most of the conventional treatment modalities, boosts their efficacy, and helps to resensitize cells to previously ineffective treatments.

There are a great number of books devoted to the efficacy and the power of hyperthermia in oncology [1–20]. However, despite its long history, the state of oncological hyperthermia today is similar to that of the therapies in their infancy. Like many early-stage therapies, it lacks adequate treatment experience and long-term, comprehensive statistics that can help us optimize its use for all indications. The promise of hyperthermia applications in oncology is high, and it has shown numerous positive impacts together with all the conventional and emerging new oncotherapies. The picture is very positive and it looks plausible that the method is at the center of interest among the specialists in oncology and related medical fields. But in fact, it is not! Doubts shadow the bright picture. Despite the large number of excellent published clinical results, the challenge of hyperthermia in oncology is understandable from the perspective of a few thousand years. Medicine faces unsolved problems in hyperthermia, mainly, because of its controversial results obtained from the very beginning. While the mechanisms of hyperthermia are unexplained, its optimal control for efficacy and for safety remains unresolved as well.

The challenges look technically simple:

(i) deliver the heat to deep targets in the body;

Oncothermia research at preclinical level

G. Andocs[1], Y. Okamoto[1], T. Osaki[1], T. Tsuka[1], T. Imagawa[1], S. Minami[1], L. Balogh[2], N. Meggyeshazi[3], and O. Szasz.[4]

(1) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Minami, Koyama-Cho, Tottori 4-101, Japan

(2) "Frederic Joliot Curie," National Research Institute for Radiobiology and Radiohygiene, Anna u. 5, Budapest 1221, Hungary

(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Ulloi ut 26, Budapest 1085, Hungary

(4) Biotechnics Department, Faculty of Engineering, St. Istvan University, Pater K. u. 1, Godollo 2100, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 272467, 9 pages
http://dx.doi.org/10.1155/2013/272467

Conference Paper

Oncothermia Research at Preclinical Level

G. Andocs,[1] Y. Okamoto,[1] T. Osaki,[1] T. Tsuka,[1] T. Imagawa,[1] S. Minami,[1] L. Balogh,[2] N. Meggyeshazi,[3] and O. Szasz[4]

[1] *Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Minami, Koyama-Cho, Tottori 4-101, Japan*
[2] *"Frederic Joliot Curie," National Research Institute for Radiobiology and Radiohygiene, Anna u. 5, Budapest 1221, Hungary*
[3] *1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Ulloi ut 26, Budapest 1085, Hungary*
[4] *Biotechnics Department, Faculty of Engineering, St. István University, Pater K. u. 1, Godollo 2100, Hungary*

Correspondence should be addressed to G. Andocs; gandocs@gmail.com

Received 2 June 2013; Accepted 12 July 2013

Academic Editors: G. Baronzio, D. Y. Lee, and A. Szasz

This Conference Paper is based on a presentation given by G. Andocs at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

We describe a new electrohyperthermia (oncothermia) method and a tumor treatment system, which was developed to cure companion animals having spontaneously occurring tumors. This dedicated veterinary oncothermia device plays a dual role; this can be a new hope to successfully treat companion animals having tumors. And during these treatments, we can get a large amount of valuable information about the real nature and parameter of the applied electromagnetic field and the behaviour of the tumor under this special modulated radiofrequency field. Then, this experience and knowledge can be transferred directly to the human clinical application to develop more precise treatment systems for human clinical oncology.

1. Background

Oncothermia method (OTM) is a long-time (since 1989) applied electrohyperthermia treatment modality in human clinical oncology [1]. Its clinical results are excellently showing the advantages of the method [2]; however, the details of its mechanism of action are intensively investigated even now. Oncothermia research group conducts investigations at all levels of scientific research, from in vitro studies to human clinical trials [3]. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven in vivo [4], but the complex electromagnetic parameters playing crucial role to achieve these antitumor effects had not yet exactly been determined.

On the other hand, in the veterinary oncology practice there is a huge need for an effective treatment to cure malignant diseases due to the increasing incidence of cancer in pet animals [5]. In the past decades, a lot of hyperthermia methods were developed for human oncological treatments, and many of them were also tested in the field of the veterinary clinical practice. Whole body hyperthermia was used with limited success due to the serious side effects [6–9]; therefore, locoregional hyperthermia techniques became more prevalent. These techniques use the energy of the electromagnetic field to heat up the tumors. Several different radiofrequency (RF) methods were tested, like local current field technology which was very successful to treat surface-localized tumors [10–12]. Interstitial hyperthermia methods when metal needles were placed invasively into the tumor, and RF current was applied via the needles [13, 14]. Microwave (MW) technologies were also tried in veterinary hyperthermia with varying clinical success [15–17]. The most interesting capacitively coupled RF technology was described in [18] where the tumor was heated up selectively with great efficacy. Unfortunately, this very promising technology was forgotten.

Presently, contrary to the huge demand, in the veterinary practice, there is no any really effective, relatively cheap,

Hyperfractionated Thermoradiotherapy (HTRT) is more effective and less invasive then radiation or chemoradiation in heatable

Haim I. Bicher[1]
(1) Bicher Cancer Institute, 12099W.Washington Boulevard, Los Angeles, CA 90066, USA

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 879513, 4 pages
http://dx.doi.org/10.1155/2013/879513

Hindawi

Conference Paper

Hyperfractionated Thermoradiotherapy Is More Effective and Less Invasive Than Radiation or Chemoradiation in Heatable Cancers: A Meta-Analysis

Haim I. Bicher

Bicher Cancer Institute, 12099 W. Washington Boulevard, Los Angeles, CA 90066, USA

Correspondence should be addressed to Haim I. Bicher; james.bicher@bci-vci.org

Received 24 January 2013; Accepted 8 July 2013

Academic Editors: G. Baronzio, M. Jackson, D. Y. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Haim I. Bicher at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

HTRT consists of daily hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180 to 100 cGy resulting in protracted treatment time that decreases the isoeffect biological equivalent dose by 15% to 25%. This decrease is compensated by the increased number of hyperthermia fractions which potentiates each radiation dose. Treatment is continued until an objective complete response is attained, or failure determined. Sixty breast patients, 35 head and neck, and 25 prostate patients were treated with a followup of two to five years. All patients were early stage (less than III). HTRT proved to be less toxic and more effective than radiation or chemoradiation therapies.

1. Introduction

Hyperthermia, applied regionally, is a potent sensitizer of radiation therapy in the treatment of cancerous tumors [1–10] and as such has been used as a palliation measure [11–13] or more recently with curative intent [14]. The ability of Hyperthermia to reoxygenate tumor tissue makes hypoxic tumors, such as sarcomas or glioblastomas, more responsive to radiation [15]. In a prior publication [14], we discussed good therapeutic results (over 80% 5-year survival) using Hyperfractionated Thermoradiotherapy (HTRT) in heatable superficial tumors. In the current investigation, we report on an expanded series of patients as well as performing a meta-analysis comparing HTRT with external beam radiation (EBRT) or chemoradiation.

2. Material and Methods

Hyperthermia was delivered using either microwaves (BSD-100 or Cheng Laboratories) or ultrasound (Labthermics) FDA-approved equipment with appropriate applicators. Thermometry was done using microthermocouples placed in the tumor region (BCIW, LA, and CA); for prostate tumors only ultrasound was used. Radiation was delivered by a 12 MEV Siemens Mevatron Machine adapted for IMRT and IGRT with a LinaTech system for computer planning and collimator alteration. Fractionation used involved daily hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180 cGy to 100 cGy resulting in the isoeffect biological equivalent dose lower by 15% to 25%, according to Ellis TDF formula.

This decrease is compensated by the increased number of hyperthermia fractions which potentiates each radiation dose. Treatment is continued until an objective complete response is attained, or failure determined. Forty breast patients, 27 head and neck, and 22 prostate patients were treated with a followup of two to five years. All patients were early stage (III-a or less); the total dose is adapted to the clinical situation. To this effect, the use of objective end results parameters is introduced, including MRI, MR spectroscopy [16], PET scanning, tumor markers, and PSA levels. Typically,

Programmed cell death induced by modulated electro-hyperthermia

Meggyesházi Nóra[1], Andócs Gábor[2], and Krenács Tibor[1]
(1) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori 680-8553, Japan

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 187835, 3 pages
http://dx.doi.org/10.1155/2013/187835

Conference Paper

Programmed Cell Death Induced by Modulated Electrohyperthermia

Meggyesházi Nóra,[1] Andócs Gábor,[2] and Krenács Tibor[1]

[1] *1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary*
[2] *Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori 680-8553, Japan*

Correspondence should be addressed to Krenács Tibor; krenacst@gmail.gom

Received 22 January 2013; Accepted 7 July 2013

Academic Editors: G. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Meggyesházi Nóra at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Background. Modulated electrohyperthermia (mEHT) is a noninvasive technique for targeted tumor treatment. *Method.* HT29 human colorectal carcinoma cell line xenografted to both femoral regions of BalbC/nu/nu mice was treated with a single shot OTM treatment. Histomorphologic, immunohistochemical analysis TUNEL assay, and R&D Apoptosis array were performed on tissue samples. *Results.* mEHT caused a selective tumor demolition. An upregulation of TRAIL-R2 and FAS was observed. Cleaved caspase-3 positive cells appear at the tumor periphery. Cytochrome c and AIF release was observed in line with massive TUNEL positivity. *Conclusion.* In HT29 colorectal cancer xenograft, mEHT caused massive caspase independent cell death.

1. Background

Modulated electrohyperthermia (mEHT) is a noninvasive technique for targeted tumor treatment [1–4]. The capacitive coupled modulated radiofrequency enriches in the tumor tissue, because of its dielectric differences [5, 6], without harming the surrounding nonmalignant tissues. The possible mechanism of action of conventional hyperthermia on tumor models was previously slightly investigated and has not been fully evaluated [7]. Already it was shown that mEHT has nontemperature dependent effect beside the temperature dependent one [8]. Here, our aim was to detect the possible role of mEHT in tumor cell death.

2. Method

HT29 human colorectal carcinoma cell line xenografted to both femoral regions of BalbC/nu/nu mice was treated with a single shot OTM treatment (LabEHY, Oncotherm Ltd, Páty, Hungary) for 30 minutes of approximately 1.5 cm diameter tumors. Sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, and 216 h in 3 mice, each group by keeping 5 untreated animals. The temperature measurement was carried out during the treatment using optical probes (Luxtron FOT Lab Kit, LumaSense Technologies, Inc., CA, USA). The treated tumor core the treated tumor surface subcutaneously, the untreated tumor core and the rectal temperature was measured. The treated tumore core temperature was 41-42°C during the treatment. Histomorphologic (H&E), immunohistochemical analysis by cleaved caspase-3 (Cell Signaling, Danvers, MA), TRAIL-R2 (Cell Signaling), cytochrome c (Cell Signaling), and AIF (Cell Signaling) were completed on formalin fixed paraffin embedded tissue microarrays (TMA, TMA Master, 3DHISTECH Ltd., Budapest, Hungary) prepared from all samples. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay (Invitrogen, Carlsbad, CA) was performed on TMA at 24 h and 48 h after treatment of whole sections. R&D Apoptosis array (R&D, Minneapolis, MN) was carried out on the 8 h, 14 h, and 24 h treated and 24 h untreated samples. Results were analyzed using digital microscopy and were evaluated by ImageJ.

Deep temperature measurements in oncothermia processes

Gabor Nagy[1], Nora Meggyeshazi[2], and Oliver Szasz[1,3]
(1) Oncotherm Kft, Ibolya u. 2., 2071 Paty, Hungary
(2) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Ulloi ut 26., 1085 Budapest, Hungary
(3) Department of Biotechnics, Faculty of Engineering, St. Istv´an University, Pater K. u. 1., 2100 Godollo, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 685264, 6 pages
http://dx.doi.org/10.1155/2013/685264

Conference Paper

Deep Temperature Measurements in Oncothermia Processes

Gabor Nagy,[1] Nora Meggyeshazi,[2] and Oliver Szasz[1,3]

[1] *Oncotherm Kft, Ibolya u. 2., 2071 Paty, Hungary*
[2] *1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Ulloi ut 26., 1085 Budapest, Hungary*
[3] *Department of Biotechnics, Faculty of Engineering, St. István University, Pater K. u. 1., 2100 Godollo, Hungary*

Correspondence should be addressed to Gabor Nagy; nagygabor@oncotherm.org

Received 21 January 2013; Accepted 7 May 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Gabor Nagy at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Temperature in depth of various model systems was measured, starting with muscle and other phantoms. It was shown that the temperature can be selectively increased in the target. In water-protein phantom, the protein coagulation (>60°C) was observed selectively while the water temperature around it was a little higher than room temperature.

1. Introduction

Research of oncothermia has wide range of temperature measurements since its origin in 1988. Numerous experiments were done in various model systems and phantoms, including various ex vivo tissues and complex body parts of various animals [1]. Independently from Oncotherm, the temperature development was also measured in a complex meat phantom [2].

New model experiments have been recently performed to show the depth profile of heating and to be sure of the deep heating facility by oncothermia devices. Some devices use the size of the electrode pair for focusing, suggesting that the small electrodes have less penetration. Generally it is true in the radiative approach, but our impedance heating is different. We used the smallest available electrode (10 cm diameter) showing that even with this the impedance heating is effective in depth.

The problem of the controlled and focused heat delivery to deep-seated tissues is a long-standing problem of the local hyperthermia in oncology [3]. The multiple artificial methods to focus the temperature have numerous technical and physiological problems. The energy could be focused in a planned and accurate way, but the temperature spreads naturally. One further problem is the physiological control in living objects, which is likely to act by negative feedback, limiting, or blocking the temperature increase during the actual heating process.

2. Methods

The early (twenty years old) phantom measurements have been repeated under much more modern conditions and have been checked with optical fiber thermosensing method, and also the outside heating profile has been controlled for visual pattern by a high-sensitivity thermocamera system. The in vivo models, as well as all the animal experiments, have used fluoroptic temperature measurements which were a Luxtron optical thermometer. We made measurements in various points of the phantoms in depth. The precise inserting of the sensors has been controlled by imaging technologies in large animals and humans. We used EHY-2000+ and a small electrode for the treatment.

Treatment of advanced cervical cancer with complex chemoradio - hyperthermia

L. Pesti[1], Zs. Dankovics[1], P. Lorencz[1], and A. Csejtei[1]
(1) Department of Oncoradiology, Non-Profit Trust. Markusovszky Hospital, Vas Country, Szombathely, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 192435, 4 pages
http://dx.doi.org/10.1155/2013/192435

Conference Paper

Treatment of Advanced Cervical Cancer with Complex Chemoradio-Hyperthermia

L. Pesti, Zs. Dankovics, P. Lorencz, and A. Csejtei

Department of Oncoradiology, Non-Profit Trust, Markusovszky Hospital, Vas County, Szombathely, Hungary

Correspondence should be addressed to A. Csejtei; csejtei.andras@markusovszky.hu

Received 21 January 2013; Accepted 18 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by L. Pesti at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

This single arm, retrospective, single institution study investigated intention to treat patients ($n = 72$) with advanced cancer of cervix of uterus. The study was performed in 2001–2010, providing 331 sessions. All patients had radiotherapies as fractional radiotherapy and intracavital brachytherapy. Some patients ($n = 34$) received chemotherapy (Cisplatin 40 mg/m^2/week; concomitantly with tele-radiotherapy) as well. Complementary to the teleradiotherapy, oncothermia was used two times a week, targeting the pelvis. Applied energy dose was 45 W, 60 min. Oncothermia was applied immediately after the infusion, when chemotherapy was also administered. Complete and partial remission were achieved in trimodal therapies for 73.5% of the patients, while we could stabilize the disease for 14.7% of the patients.

1. Introduction

Carcinoma of the cervix of uterus is the second deadly female malignancy after mammary carcinomas. Cervical cancer incident in Hungary: 21 incidences per 100,000 females (higher than the rate in Eastern Europe) and the mortality rate is 9.6/100,000 women/year, which means the deaths of 500 women a year, [1].

Hyperthermia treatments are popular for gynecological applications [2, 3]. These focus on radiotherapy combinations [4], showing highly significant benefit of hyperthermia in overall survival, disease-free survival, and local-relapse-free survival made by randomized trial [4]. A large randomized controlled clinical trial of the radiohyperthermia is published in the Lancet [5], with great success. The results were very promising [5], but the control study [6] was disappointing. The explanation may be simple; a reference point was missing [7]. The chemotherapy combination (Cisplatin + hyperthermia for previously radiated cases) also shows feasibility [8] as well as the trimodal applications for cervix [9–11]. There are large debates in the topic [12], with counterpoints [13] and contras [14]. Our objective is to treat advanced cervical tumors with a new kind of hyperthermia (oncothermia) and add new results for the professional discussions.

Our department accepts patients from the three neighboring counties (Veszprém, Zala, and Vas) for preoperative, postoperative, definitive, and palliative treatments. In addition to the applied standard professional protocols since 2001 we have the possibility to apply complementary oncothermia treatments.

2. Method

A single arm, retrospective, single institution study investigated intention to treat patients ($n = 72$) with advanced cancer of cervix of uterus for intention to treat (ITT) population. The study was performed from 2001 till 2010, involving 331 oncothermia treatment sessions.

After a complete medical check-up upon the decision of the conference of professionals (OncoTeam), the treatment protocol was prescribed and the patients were hospitalized. Patients with solid diagnostic proofs of advanced cervix carcinoma were involved in the study. The chemoradio-therapy was administered according to the standard protocol,

Critical Analysis Of Electromagnetic Hyperthermia Randomized Trials: Dubious Effect And Multiple Biases

Sergey Roussakow[1]
(1) Galenic Research Institute, Moscow, Russia

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 192435, 4 pages
http://dx.doi.org/10.1155/2013/192435

Conference Paper

Treatment of Advanced Cervical Cancer with Complex Chemoradio-Hyperthermia

L. Pesti, Zs. Dankovics, P. Lorencz, and A. Csejtei

Department of Oncoradiology, Non-Profit Trust, Markusovszky Hospital, Vas County, Szombathely, Hungary

Correspondence should be addressed to A. Csejtei; csejtei.andras@markusovszky.hu

Received 21 January 2013; Accepted 18 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by L. Pesti at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

This single arm, retrospective, single institution study investigated intention to treat patients ($n = 72$) with advanced cancer of cervix of uterus. The study was performed in 2001–2010, providing 331 sessions. All patients had radiotherapies as fractional radiotherapy and intracavital brachytherapy. Some patients ($n = 34$) received chemotherapy (Cisplatin 40 mg/m^2/week; concomitantly with tele-radiotherapy) as well. Complementary to the teleradiotherapy, oncothermia was used two times a week, targeting the pelvis. Applied energy dose was 45 W, 60 min. Oncothermia was applied immediately after the infusion, when chemotherapy was also administered. Complete and partial remission were achieved in trimodal therapies for 73.5% of the patients, while we could stabilize the disease for 14.7% of the patients.

1. Introduction

Carcinoma of the cervix of uterus is the second deadly female malignancy after mammary carcinomas. Cervical cancer incident in Hungary: 21 incidences per 100,000 females (higher than the rate in Eastern Europe) and the mortality rate is 9.6/100,000 women/year, which means the deaths of 500 women a year, [1].

Hyperthermia treatments are popular for gynecological applications [2, 3]. These focus on radiotherapy combinations [4], showing highly significant benefit of hyperthermia in overall survival, disease-free survival, and local-relapse-free survival made by randomized trial [4]. A large randomized controlled clinical trial of the radiohyperthermia is published in the Lancet [5], with great success. The results were very promising [5], but the control study [6] was disappointing. The explanation may be simple; a reference point was missing [7]. The chemotherapy combination (Cisplatin + hyperthermia for previously radiated cases) also shows feasibility [8] as well as the trimodal applications for cervix [9–11]. There are large debates in the topic [12], with counterpoints [13] and contras [14]. Our objective is to treat advanced cervical tumors with a new kind of hyperthermia (oncothermia) and add new results for the professional discussions.

Our department accepts patients from the three neighboring counties (Veszprém, Zala, and Vas) for preoperative, postoperative, definitive, and palliative treatments. In addition to the applied standard professional protocols since 2001 we have the possibility to apply complementary oncothermia treatments.

2. Method

A single arm, retrospective, single institution study investigated intention to treat patients ($n = 72$) with advanced cancer of cervix of uterus for intention to treat (ITT) population. The study was performed from 2001 till 2010, involving 331 oncothermia treatment sessions.

After a complete medical check-up upon the decision of the conference of professionals (OncoTeam), the treatment protocol was prescribed and the patients were hospitalized. Patients with solid diagnostic proofs of advanced cervix carcinoma were involved in the study. The chemoradio-therapy was administered according to the standard protocol,

New cancer paradigm and new treatment: the example of METABLOC

Laurent Schwartz[1], Mireille Summa[2], Jean Marc Steyaert[1], Adelilne Guais-Vergne[3], and Gian Franco Baronzio[4]

(1) Ecole Polytechnique, Palaiseau, 91128 Paris, France
(2) CEREMADE Universit´e ParisDauphine, 1 PlDuMal De Lattre de Tassigny, 75016 Paris, France
(3) BIOREBUS, 66 avenue des Champs-Elys´ees lot 41, 75008 Paris, France
(4) METABLOC Research Center, Centro Medico Kines, Castano Primo (MI), Italy

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 827686, 5 pages
http://dx.doi.org/10.1155/2013/827686

Conference Paper

New Cancer Paradigm and New Treatment: The Example of METABLOC

Laurent Schwartz,[1] Mireille Summa,[2] Jean Marc Steyaert,[1] Adeline Guais-Vergne,[3] and Gian Franco Baronzio[4]

[1] *Ecole Polytechnique, Palaiseau, 91128 Paris, France*
[2] *CEREMADE Université Paris Dauphine, 1 Pl Du Mal De Lattre de Tassigny, 75016 Paris, France*
[3] *BIOREBUS, 66 avenue des Champs-Elysées lot 41, 75008 Paris, France*
[4] *METABLOC Research Center, Centro Medico Kines, Castano Primo (MI), Italy*

Correspondence should be addressed to Laurent Schwartz; laurent.schwartz@polytechnique.fr

Received 18 January 2013; Accepted 3 April 2013

Academic Editors: M. Jackson, D. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Laurent Schwartz at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Hyperthermia has long been known to interfere with the tumor metabolism. The goal of this paper is to review the potential of metabolic therapy and to suggest that its combination with hyperthermia may be of interest.

1. Objective

In a land mark article, John Bailar published in the "New England Journal of Medicine" in 1997 "Are we losing the war on cancer?" We recently confirmed that this is, still the case. We obtained from the World Health Organization mortality time-series data of 20 countries over 45 years (1961–2005). During these 45 years the age standardised cancer death rate has varied little (−4%). There has been a slight decrease in breast cancer (−6.5%), lung cancer in men (−2.5%), and prostate cancer (−1.7%), but a sharp decrease in stomach cancer (−77%). These data confirm the preliminary results from Bailar and contradict the notion of a breakthrough in cancer prevention, early detection, and cancer treatment (Summa 2012). Today, as before, metastatic cancer to the notable exception of some childhood malignancies and of lymphoma remains almost universally fatal.

Today cancer is thought as an invasion by malignant cells which deserves to be killed either by surgery, radiation therapy, or chemotherapy. The screening of new drugs is done by assessing their efficacy in killing cancer cells. Modern drugs target one specific pathway in order to kill the malignant cell. But the logic is still the same: killing the cancer cell. None of these new drugs can be credited with having changed significantly the survival pattern. For example the overall response rate to Herceptin (a so called magic bullet) when administered alone is less than 5%.

In the meantime the cost of cancer drugs has increased exponentially. It is highly probable that we are witnessing a "bubble" based more on goodwill and hope than results.

There is an obvious need for change of paradigm.

Cancer is widely thought to be the consequence of genetic abnormalities such as oncogene activation or tumor suppressor inactivation. This is correct but only a partial view of the disease. For example, there is oncogene activation in normal cells or during development or benign inflammation.

There are alternative ways of understanding cancer. The most promising is considering cancer as a metabolic disease as a disease related to diabetes.

2. Metabolic Aspects of Cancer: Otto Warburg

Cancer is not only a genetic disease but also a disease of the metabolism. Since the work of Nobel Prize winner Otto

Oncothermia as personalized treatment option

Oliver Szasz[1], Gabor Andocs[2], and Nora Meggyeshazi[3]
(1) Department of Biotechnics, St. Istvan University, Pater K. u. 1, 2100 Gödöllő, Hungary
(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Minami, Koyama-Cho, Tottori, Japan
(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Ulloi UCt 26, 1085 Budapest, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 941364, 6 pages
http://dx.doi.org/10.1155/2013/941364

Conference Paper

Oncothermia as Personalized Treatment Option

Oliver Szasz,[1] Gabor Andocs,[2] and Nora Meggyeshazi[3]

[1] *Department of Biotechnics, St. Istvan University, Pater K. u. 1, 2100 Gödöllő, Hungary*
[2] *Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Minami, Koyama-Cho, Tottori, Japan*
[3] *1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Ulloi UCt 26, 1085 Budapest, Hungary*

Correspondence should be addressed to Oliver Szasz; droliverszasz@gmail.com

Received 18 January 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, D. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Oliver Szasz at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Oncothermia is a nanoheating technology personalized for individual status depending on the state, stage, grade, and other personal factors. The guiding line of the treatment keeps the homeostatic control as much effective as possible. One of the crucial points is the surface heat regulation, which has to be carefully done by the electrode systems. The applied stepup heating supports the physiological selection. Recognizing the hysteresis type of SAR-temperature, development of the protocol could be well conducted. Using the Weibull distribution function of the transport processes as well as considering the typical physiological relaxation time of the tissues, special protocols can be developed. It has wide-range applicability for every solid tumor, irrespective of its primary or metastatic form. It could be applied complementary to all the known oncotherapy methods. It is applicable in higher lines of the therapy protocols, even in the refractory and relapsed cases as well.

1. Introduction

The personalization of the oncological treatments is the new trend in modern medicine [1]. Oncothermia is a personalized treatment using energy delivery to the targeted tumor [2]. This energy is well focused on cellular level [3] and makes the dose of energy optimal for cell destruction [4]. The personal feedback of the patient together with the natural homeostatic control of the treatment actions makes the treatment realistically personalized [5]. The central task is to find the proper dose in the given application and optimize the safety and curative limits of the applied dose. The lower limit is of course determined by the minimal effect by heating and the upper limit determined mainly by the safety issues, like it is usual for overdoses. The lower limit of oncothermia dose is indefinite because in case of normothermia nothing else has action except the complementary treatment alone, which has no danger and has such curative effect as we expect from the gold standards. For the upper limit, however, there are very definite technical and physiological parameters: the surface power density of the signal is limited by the blistering to 0.5 W/cm^2, (60 min basis), the internal hot-spots could hurt the healthy tissue, and in systemic application the physiology anyway is limited at 42°C. The ultimate challenge is the developing heat resistance, which could make the hyperthermia ineffective and the disease refractory to heating. The presently applied dose concept (CEM) in conventional hyperthermia is physically incorrect (temperature is not a dose), and due to its inhomogeneity concept it is hard to measure. The systemic (whole body) heating in extreme case reaches 42°C (even 43°C is applied sometimes in special conditions; CEM 100%), but the expected distortion of the tumor does not happen. The high energy of the local heating (in most of the cases more than 1kW is applied) at the start makes vasodilatation, which turns to vasocontraction over a definite physiological threshold at about 40°C. In consequence, over this threshold the high temperature blocks the complementary drug delivery and causes severe hypoxia, which is a severe suppression of the effect of complementary radiotherapy. Furthermore, the conductivity and permittivity

Oncothermia with Chemotherapy in the patietns with Small Cell Lung Cancer

Doo Yun Lee[1], Seok Jin Haam[1], Tae Hoon Kim[2], Jae Yun Lim[3], Eun Jung Kim[1], and Na Young Kim[1,]

(1) Department ofThoracic & Cardio-Vascular Surgery, Gangnam Severance Hospital, College of Medicine, Yonsei University, Seoul 120-752, Republic of Korea

(2) Department of Diagnostic Radiology, Gangnam Severance Hospital, College of Medicine, Yonsei University, Seoul 120-752, Republic of Korea

(3) Department of Medical Oncology, Gangnam Severance Hospital, College of Medicine, Yonsei University, Seoul 120-752, Republic of Korea

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 910363, 7 pages
http://dx.doi.org/10.1155/2013/910363

Conference Paper

Oncothermia with Chemotherapy in the Patients with Small-Cell Lung Cancer

Doo Yun Lee,[1] Seok Jin Haam,[1] Tae Hoon Kim,[2] Jae Yun Lim,[3] Eun Jung Kim,[1] and Na Young Kim[1]

[1] *Department of Thoracic & Cardio-Vascular Surgery, Gangnam Severance Hospital, College of Medicine, Yonsei University, Seoul 120-752, Republic of Korea*
[2] *Department of Diagnostic Radiology, Gangnam Severance Hospital, College of Medicine, Yonsei University, Seoul 120-752, Republic of Korea*
[3] *Department of Medical Oncology, Gangnam Severance Hospital, College of Medicine, Yonsei University, Seoul 120-752, Republic of Korea*

Correspondence should be addressed to Doo Yun Lee; dylee@yuhs.ac

Received 18 January 2013; Accepted 3 April 2013

Academic Editors: G. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Doo Yun Lee at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Small-cell lung cancer (SCLC) is one of the most aggressive and lethal forms of lung cancers. Chemotherapy and radiotherapy would be standard modality for SCLC with median survival being less than 4 months only. Complementary treatment to chemotherapy is desired. Oncothermia will be one of the candidates to this addition. We have made a study of 31 SCLC patients from April 2006 to March 2012. 23 cases were treated with combined chemotherapy and oncothermia, and 8 cases were treated with chemotherapy alone. Three patients from 14 patients (14/31) died in the study period; there were equal numbers in the two arms, including one long survival case of 28 months and one of 26 months, in the combination and chemo-group, respectively .16 patients (16/31) are alive: 4 patients with chemotherapy only, including one long survival case of 28.7 months, and 11 cases with combined therapy including three long survival cases of more than 3 years. We conclude that the combined use of chemotherapy and oncothermia has significantly enhanced the survival rate in comparison with the use of chemotherapy alone (log-rank test: P value < 0.02).

1. Introduction and Background

Lung cancer is one of the most common causes of cancer-related deaths in both men and women worldwide. Its incidence as well as mortality rates is high, and the prognosis is usually very poor [1]. Its age-standardized incidence and mortality rates in 2006 were estimated to be 75.3 and 64.8/100 000/year, respectively, in men and 18.3 and 15.1/100 000/year in women in Europe, where the small-cell lung cancer (SCLC) accounts for 15%–18% of all cases [2]. The small-cell lung cancer has a fast growth-rate, disseminated quickly around the mediastinal lymph nodes, and forms distant metastases in late diagnosis, and then the median survival is only 2–4 months; the overall prognosis is very poor [3, 4].

Surgical treatment is not possible in almost all SCLC cases; it could be performed in very limited stage of the disease (i.e. T1,N0) only [2]; consequently the main treatments are chemo- and radiotherapy. The overall 2-year survival rate is less than 20%; and 5-year survival rate is almost devoid. In 50% of relapse SCLC cases chemotherapy reached complete remission (CR). In these the bulky primary tumors were completely destroyed but most intrathoracic recurrence was difficult to discover. In cases when radiotherapy was added, [5], recurrence rate has been reduced in 30–60% of the cases, however radiation pneumonitis, esophagitis was observed,

Oncothermia basic research at in vivo level. The first results in Japan

G. Andocs[1], Y. Okamoto[1], K. Kawamoto[1], T. Osaki[1], T. Tsuka[1], T. Imagawa[1], S. Minami[1], L. Balogh[2], N. Meggyeshazi[3], and O. Szasz[4]

(1) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Koyama Minami Tottori 680-8553, Japan

(2) "Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, XXII. Ker. Anna u. 5, 1221 Budapest, Hungary

(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, ¨ Ullői út 26, 1085 Budapest, Hungary

(4) Biotechnics Department, Faculty of Engineering, St. István University, Pater K. u. 1., 2100 Godollo, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 197328, 6 pages
http://dx.doi.org/10.1155/2013/197328

Conference Paper

Oncothermia Basic Research at In Vivo Level: The First Results in Japan

G. Andocs,[1] Y. Okamoto,[1] K. Kawamoto,[1] T. Osaki,[1] T. Tsuka,[1] T. Imagawa,[1] S. Minami,[1] L. Balogh,[2] N. Meggyeshazi,[3] and O. Szasz[4]

[1] *Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Koyama Minami, Tottori 680-8553, Japan*
[2] *"Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, XXII. Ker. Anna u. 5, 1221 Budapest, Hungary*
[3] *1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Üllői út 26, 1085 Budapest, Hungary*
[4] *Biotechnics Department, Faculty of Engineering, St. István University, Pater K. u. 1., 2100 Godollo, Hungary*

Correspondence should be addressed to G. Andocs; gandocs@gmail.com

Received 17 January 2013; Accepted 28 May 2013

Academic Editors: G. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by G. Andocs at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

This paper summarizes the first results of oncothermia basic research conducted in Tottori University, Japan, and had two parts. In the first part C26 murine colorectal cancer model was investigated and oncothermia treatment induced histomorphological and some molecular changes which were examined. In the second study 9L rat glioma model was used to investigate the oncothermia treatment effects on tumor tissue oxygenization. Results of these investigations are very important in oncothermia research because this was the first time when independent research laboratory has repeated oncothermia experiments and proved the significant antitumoral and beneficial effects of oncothermia treatment.

1. Background

Oncothermia method (OTM) is a long time (since 1989) applied method in oncology [1] with great clinical success [2]. Oncothermia research group conducts investigations to reveal the basic mechanism of action of this tumor treatment method in basic research level performing a huge number of in vivo studies. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven earlier and presented elsewhere [3, 4], as well as the recent in vivo results [5, 6]. In this paper we summarize the first results we have achieved in Tottori University, Japan.

2. Materials and Methods

2.1. Study I. In the first study we examine the effect of oncothermia treatment in a mouse tumor model.

2.1.1. Animal Model. Colon 26 (murine colorectal cancer) cell line derived allograft mouse tumor model was used for this study with double tumors (see Figure 1). The use of the mice and the procedures used in this study were approved by the Animal Research Committee of Tottori University.

2.1.2. Experimental Setup and Treatment. A single shot 30 min oncothermia treatment was done reaching maximum 42°C intratumoral temperature, using the LabEHY system (Oncotherm Ltd.), under precise tumor temperature control using fluoroptic temperature measurement device (Lumasense m3300) (see Figure 2).

2.1.3. Study Design. Time course study was performed. After a single shot oncothermia treatment, animals were sacrificed at 6H, 24H, 72H, and 120H later and tumors were removed.

Essentials of oncothermia

Oliver Szasz
(1) Department of Biothecnics, Szent Istvan University, Pater K. u. 1., Godollo 2100, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 159570, 20 pages
http://dx.doi.org/10.1155/2013/159570

Hindawi

Conference Paper

Essentials of Oncothermia

Oliver Szasz

Department of Biotechnics, Szent Istvan University, Pater K. u. 1., Godollo 2100, Hungary

Correspondence should be addressed to Oliver Szasz; droliverszasz@gmail.com

Received 17 January 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, D. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Oliver Szasz at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Oncothermia is a method of hyperthermia in oncology, controlling the locally applied deep heat by selectively targeting the cellular membrane of the malignant cells. The selection of the method is based on various biophysical and biochemical achievements. There are various differences between the malignant and healthy cells, which could be used for their selection by heat targeting. The primary selection factor is a different metabolic activity which creates distinguishable environments of the malignant cells. The other factor is the clear difference of dielectric properties of the membrane and near-membrane extracellular electrolytes, marking off the malignancies. There is also a structural factor, which is clear in the different pathological patterns of the malignancy from their healthy counterparts. This last is described by fractal pattern evaluation technique, in which dynamic time-fractal transformation is used for further discernment of the malignancy. My objective is to show a new heating method, which makes oncological hyperthermia controllable and effective.

1. Introduction

Oncological hyperthermia is the overheating of the malignant tissues locally or systemically. The method is deduced from the ancient medical practices, where the heat therapies had a central role in medicine. The local hyperthermia by the radiation of red-hot iron was the first known oncological treatment applied by Hypocrites, who described the method [1]. The main idea was originated from sacral considerations formulating the overall force of the "fire." However, physiological consideration was also behind that together with beliefs: the local heat accelerates the metabolic activity without extra supply of this action from the unheated neighboring volumes. This physiological mechanism is accompanied by severe hypoxia, and it finally kills the target by acidosis. The working idea has recently been shown, proving the impoverishment of ATP and enrichment of lactate in the locally heated tumor tissue [2]. Due to the primitive heating techniques, the ancient radiative heat is only rarely applied in real cases. The central point of the locally applied oncological hyperthermia is the selective heat delivery into the deep-seated tumors. The discovery of the electromagnetic heating gave new perspectives for deep heating, and hyperthermia started its first "golden era" in oncology. It was among the first modern curative applications of modern techniques in oncology [3] and was followed by a controlled clinical study involving 100 patients as early as 1912. It showed remarkable benefit of the combined thermoradiation therapy [4]. The method was further developed in three various branches: the interstitial hyperthermia, including the galvanic heat stimulation, the ablation techniques, and the capacitive coupling. The first capacitive coupled device was launched by Siemens. The skeptical opinion about oncological hyperthermia was also typical: "All of these methods impress the patient very much; they do not impress their cancer at all" [5]. After a small dormant period, the phoenix life of hyperthermia in oncology started again. The first start of the new capacitive-coupling technologies was by LeVeen et al. [6] in 1976 and has been widely applied since then [7, 8]. Its efficacy was discussed and proven in the relevant literature in its time [9–13].

Treatments with coils (magnetic and inductive) are relatively rarely used due to the negligible magnetic permeability of living systems [14]. In order to improve the magnetic

Bystander effect of oncothermia

G. Andocs[1], N. Meggyeshazi[2], Y. Okamoto[1], L. Balogh[3], and O. Szasz[4]

(1) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Koyama Minami, Tottori 680-8553, Japan

(2) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Üllői út 26., 1085 Budapest, Hungary

(3) "Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, XXII. Ker. Anna u. 5., 1221 Budapest, Hungary

(4) Biotechnics Department, Faculty of Engineering, St. István University, Pater K. u. 1., 2100 Godollo, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 953482, 6 pages
http://dx.doi.org/10.1155/2013/953482

Conference Paper

Bystander Effect of Oncothermia

G. Andocs,[1] N. Meggyeshazi,[2] Y. Okamoto,[1] L. Balogh,[3] and O. Szasz[4]

[1] *Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Koyama Minami, Tottori 680-8553, Japan*
[2] *1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Üllői út 26., 1085 Budapest, Hungary*
[3] *"Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, XXII. Ker. Anna u. 5., 1221 Budapest, Hungary*
[4] *Biotechnics Department, Faculty of Engineering, St. István University, Pater K. u. 1., 2100 Godollo, Hungary*

Correspondence should be addressed to G. Andocs; gandocs@gmail.com

Received 17 January 2013; Accepted 28 May 2013

Academic Editors: G. Baronzio, M. Jackson, D. Y. Lee, and A. Szasz

This Conference Paper is based on a presentation given by G. Andocs at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Metastatic form of malignant tumor diseases is the most serious problem in oncology and the greatest challenge in tumor therapy. Conventional therapeutical approaches (surgery, irradiation, and chemotherapy) cannot manage this challenge in oncological practice. According to our theory, oncothermia treatment-induced immunogenic tumor cell death can be a very good basis for immunotherapy combination to make systemic tumor control from a local tumor destruction effect. We summarize the molecular basis of the oncothermia treatment-induced immunogenic cell death as a necessary basic condition to achieve the bystander effect.

1. Background

Oncothermia (OTM) is an electrohyperthermia modality, a long-time (since 1989) applied method in oncology, [1] with great clinical success [2]. OTM changes the paradigm of hyperthermia by targeted microscopic heat liberation at the membrane of the malignant cells. This method creates inhomogeneous heating, microscopic temperature differences far from thermal equilibrium. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven earlier by laboratory research and presented elsewhere [3, 4].

Bystander effect (abscopal effect) means that a local tumor treatment can affect the behavior of the far distant metastases. It was first discovered by radiooncologists and remained a higly controversial topic until recent years [5, 6]. Intensive research is conducting to reveal the immunbiological basis [7–9] and mechanism of action of this effect [10] and using the benefits in the regular oncological practice.

The objective is showing the newest results of oncothermia in research bystander effect.

2. Materials and Methods

2.1. Animal Model. HT29 human colorectal carcinoma cell line derived xenograft tumor model in nude mouse. See Figure 1.

2.2. Experimental Setup and Treatment. A single shot 30 min oncothermia treatment was done, reaching maximum 41-42°C intratumoral temperature, using the LabEHY system (Oncotherm Ltd.), under precise tumor temperature control using fluoroptic temperature measurement system (Lumasense, Luxtron m3300). See Figure 2.

2.3. Study Design. Time course study was performed. After a single shot treatment, sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, and 216 hours. Three mice were

Oncothermia application for various malignant diseases

Youngsuk Lee[1]
(1) Good World Anti Cancer Center, 542-6 Dogok-dong, Gangnam-gu, Seoul, Republic of Korea

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 245156, 6 pages
http://dx.doi.org/10.1155/2013/245156

Conference Paper

Oncothermia Application for Various Malignant Diseases

Youngsuk Lee

Good World Anti Cancer Center, 542-6 Dogok-dong, Gangnam-gu, Seoul, Republic of Korea

Correspondence should be addressed to Youngsuk Lee; englishee@hanmail.net

Received 17 January 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Youngsuk Lee at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Oncothermia was introduced to our hospital in 2010. Our objective is to report results of 277 patients treated by oncothermia during 20 months. We present some characteristic cases and statistical study of the overall results. We concluded by stating the feasibility of oncothermia to treat high variety of malignant diseases also in their very advanced (T4N3M1) stages.

1. Background

Hyperthermia is a long-time used treatment in oncology, having debates about its applicability and working mechanisms. There are numerous technical solutions [1, 2] but the results are mostly controversial like the cervix studies (the positive [3] and the opposite effects [4] of hyperthermia were published). The basic problem is the missing control, due to the simple fact of the focusing possibilities. The sophisticated technologies are concentrating the localized and focused energy on the target; however the temperature is distributed from any sharply focused volume, naturally trying to be equalized in its neighborhood. The smearing of the temperature is accelerated by the physiologic feedback to cool down the specially heated volume by the extra blood flow in the heated part of the body [5, 6]. The extra blood flow naturally supports the tumor by nutrients (mainly glucose) and increases the risk of dissemination. The focusing and heating mechanisms are certainly different in various kinds of technical solutions, which reflects the problem of the standardization; no reference point exists [7].

2. Method

Avoiding the controversies, oncothermia was used in our study. Oncothermia has realized the root of the problem: impossibility to localize the temperature in the desired volume. The solution was the nanoheating technology. Oncothermia selects and heats up very locally (in nanoscopic range) the membrane of the malignant tumors, [8]. This effect excites important pathologic pathways to promote apoptosis [9] and overcome the main problem of the technical challenge by large energy intake but on a very well-localized place. It needs 60 min to reach the general temperature equilibrium, which is the time of the active oncothermia session. The oncothermia in this line is working permanently by thermal nonequilibrium conditions.

We collected all patients ($n = 277$) who had at least one oncothermia treatment in time interval November 2010–July 2013 (20 months). The patient group had $n_M = 125$ males and $n_F = 152$ females. Average age was 53 y (7–84 y). The various diseases and the number of patients involved in the study were heterogeneous (see Figure 1) aiming to check the efficacy on the wide range of diseases and stages.

Major target areas were lung 53, stomach 33, breast 30, and colon 25. We assume the reason why lung cancer was the highest number. It is not only because lung cancer is the most common cancer in Republic of Korea but also other area's cancers easily metastasize to lung.

The treatment had step-up heating protocol (60 W → 150 W), using 20 cm and 30 cm diameter electrodes. The step-up grades were fit by personalization, with careful control of the actual patient. Oncothermia was applied 1 ~ 4 times a week (Figure 2). 47.9% of the patients got 3 times a week and the cases of 4 treatments a week was on multiple locations.

Cases that respond to Oncothermia monotherapy

Tae Sig Jeung[1], Sun Young Ma[1], Jesang Yu[1], and Sangwook Lim[1]
(1) Department of Radiation Oncology, Kosin University College of Medicina, 34 Amnan-dong, Seo-gu, Busan 602-702, Republic of Korea

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 392480, 12 pages
http://dx.doi.org/10.1155/2013/392480

Conference Paper

Cases That Respond to Oncothermia Monotherapy

Tae Sig Jeung, Sun Young Ma, Jesang Yu, and Sangwook Lim

Department of Radiation Oncology, Kosin University College of Medicine, 34 Amnam-dong, Seo-gu, Busan 602-702, Republic of Korea

Correspondence should be addressed to Tae Sig Jeung; ksung510@gmail.com

Received 17 January 2013; Accepted 29 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, D. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Tae Sig Jeung at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

There is a long history of hyperthermia in oncology, but its wide range acceptance and application are missing even today. A new approach of oncological hyperthermia, oncothermia, looks promising modality of the complementary treatment of advanced malignant cases. Our present paper is targeting this method, trying to answer the question of its feasibility to treat various advanced cases in monotherapy process, as well as its applicability for a long, large number of treatment sessions protocols.

1. Background

Although the hyperthermia was among the very first medical treatments in human medicine, this approach has ambivalent evaluation as a therapy. Hyperthermia is one of the most common therapies in "house" applications, a part of the "popular wisdom" of the traditional medicine. Heat is applied according to unwritten traditions in every culture. Heat treatment has high popularity in Korea for various preventive or curative intentions. It is applied for simple prevention or "cure" of common cold, applied to still various pains (joints, muscle spasms, various orthopedic problems, etc.). Heat is applied for better overall conditions and for simple relaxing or sometimes for spiritual reasons. The various heat therapies are commonly used complementarily with natural drugs (tees, herbs, oils, aromas, etc.) or with natural radiations (sunshine, red-hot iron radiation, etc.) This popular medicine is sometimes connected with ritual, cultural, and social events (ritual hot bath cultures) or to long-time continued chronic cures (like special spa treatments, hot-spring natural drinks, etc.).

These popular treatment applications of heating are types of "kitchen medicine": the old recipes are "sure," the patient takes it, and cured when it is done according to the auricular traditional regulations. This "for sure" is the disadvantage of the popular wisdom. It interprets this heating method as a simple causal process, "do it, get it." However, the hyperthermia is not as simple as the traditions interpret it.

Internal source of heat is the fever as a reaction to infections [1] or pyrogens [2] or malignant hyperthermia [3] as well. The natural fever is induced by the living system [4]. The situation is quite different, when the heating is forced from outside of the body, and it is intended to be applied as therapy. The forced heating works against the homeostasis, and the body tries to keep the temperature normal, irrespective that the heating is local, regional, or systemic. The interpretation of hyperthermia as therapy has various stumbling blocks, because the effect caused by the absorbed heat is too complex: the applied, absorbed energy is usually depleted nonhomogeneously, and the intricacy of the living processes modifies the intended motive of application. Further complication is in the heating process itself: the efficacy certainly differs by heat sources and by the properties of the target volume and its physiological effects as well.

A frustration in understanding of the differences between the natural and constrained heat therapies and their consequent reactions characterizes the complete history of hyperthermia in medicine and explains in majority why hyperthermia has no well-deserved place in the professional medical armory to treat various diseases.

"Quo vadis" oncologic hyperthermia?

Andras Szasz[1]
(1) Biotechnics Department, Szent Istvan University, Pater K. str., Godollo 2100, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 201671, 15 pages
http://dx.doi.org/10.1155/2013/201671

Conference Paper

"Quo Vadis" Oncologic Hyperthermia?

Andras Szasz

Biotechnics Department, Szent Istvan University, Pater K. Ulica, Godollo 2100, Hungary

Correspondence should be addressed to Andras Szasz; szasz.andras@gek.szie.hu

Received 16 January 2013; Accepted 7 July 2013

Academic Editors: G. Baronzio, M. Jackson, and D. Y. Lee

This Conference Paper is based on a presentation given by Andras Szasz at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Hyperthermia was the very first oncotherapy in human medicine based directly on sacral and philosophical roots in ancient cultures. The discovery of electromagnetism gave new hopes a century ago; however, up to now it has been suffering from lack of wide applications. Oncological hyperthermia struggles with multiple technical and medical problems which are far from the complete solution. Technically, the deep heating, the precise focusing, the technical control, and repeatability are challenging. The missing medical explanation of the phenomenon, together with the he missing measurable dose hinders the acceptance of hyperthermia. The contra-feedback of physiology mechanisms makes this method hardly controllable. Multiple, most promising results and studies are mixed together with some negatives and controversial consequences, causing huge fluctuations of its applications. There are positive and negative "believers" of the method, but the decisional facts are missing. A new way gives shape to the development: heating in nanorange, which could solve most of the open problems in oncological hyperthermia.

1. Introduction

Hyperthermia is an ancient treatment. Hyperthermia means overheating of the living object completely (systemic) or partly (regionally or locally). "Overheating" is understood as "higher temperature than normal."

Hyperthermia is one of the most common therapies in "house" applications. It is applied according to unwritten traditions in every culture and every household. It is applied simply to prevent common cold, but it is also good for its treatment, applied for various pains (joints, muscle-spasms, etc.), applied for better overall conditions and for simply relaxing, or sometimes for spiritual reasons. The various heat therapies are commonly used complementary with natural drugs (teas, herbs, oils, aromas, etc.) or with natural radiations (sunshine, red-hot iron radiation, etc.) This popular medicine is sometimes connected with ritual, cultural, and social events (ritual hot bath cultures), or with long-time continued chronic cures (like special spa treatments, hot-spring natural drinks, etc.).

The "prestige" of popular heat therapies is strongly supported by its corrective property: the person who has just received hyperthermia feels the water temperature most pleasant by hand when it is ~20°C, while the 45°C is pleasant for a hypothermic subject in the same experiment [1]. It seems that the heat therapy adjusts itself to the personal actualities; it is subjective and adaptive.

These popular treatment applications of heating are types of "kitchen medicine": the old recipes are "sure," the patient takes them and is cured when they are done according to the auricular traditional regulations. The meaning of "kitchen medicine" is, do it like in the kitchen, reading the process from the cookery-book: "heat it on the prescribed temperature for the prescribed time, and the success is guaranteed." This type of thinking has its origin from the ancient cultures, when the Sun, the fire, and the heat were somehow in the centre of the religious beliefs and philosophical focus.

This is "for sure" the disadvantage of the popular wisdom. It interprets this heating method as a simple causal process, "do it, get it." However, hyperthermia is not as simple as the traditions interpret it.

The fire and the radiation of the Sun had sacral significance in the ancient human cultures. In consequence, the heat delivery was naturally on top of the curative possibilities.

Oncothermia in HIV Positive and Negative Locally Advanced Cervical Cancer Patients in South Africa

Carrie A. Strauss[1], Jeffrey A. Kotzen[1], Ans Baeyesn[1,2], and Irma Maré[1]
(1) Radiation Sciences, University of theWitwatersrand Medical School, 7 York Road, Parktown, Johannesburg 2193, South Africa
(2) Radiation Biophysics, iThemba LABS, P.O. Box 722, SomersetWest 7129, South Africa

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 293968, 3 pages
http://dx.doi.org/10.1155/2013/293968

Conference Paper

Oncothermia in HIV-Positive and -Negative Locally Advanced Cervical Cancer Patients in South Africa

Carrie A. Strauss,[1] Jeffrey A. Kotzen,[1] Ans Baeyens,[1,2] and Irma Maré[1]

[1] *Radiation Sciences, University of the Witwatersrand Medical School, 7 York Road, Parktown, Johannesburg 2193, South Africa*
[2] *Radiation Biophysics, iThemba LABS, P.O. Box 722, Somerset West 7129, South Africa*

Correspondence should be addressed to Carrie A. Strauss; carrie@c-therm.co.za

Received 16 January 2013; Accepted 9 May 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Carrie A. Strauss at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Aim. Investigate the clinical, economic, and cellular effects of the addition of oncothermia to standard treatment for HIV-positive and -negative locally advanced cervical cancer patients in public healthcare in South Africa. *Objectives.* Evaluate the effect that the addition of oncothermia has on local disease control, progression-free survival, overall survival at 2 years, treatment toxicity, quality of life, economic impact, and HIV status of participants. Radiobiology investigations will evaluate thermoradiosensitivity and the molecular markers for thermoradiosensitivity. *Methodology.* Phase III randomised clinical trial involving 236 HIV-negative and -positive stage IIb-III locally advanced cervical cancer patients. Treatment includes cisplatin, external beam radiation, and brachytherapy. The study group will receive oncothermia treatments. Participants will be monitored for two years after completion of treatment. *Hypothesis.* The addition of oncothermia to standard treatment protocols will result in improved clinical response without increasing treatment toxicity in HIV-positive patients or raising healthcare costs.

1. Introduction

More than 80% of hospital patients in Africa receive treatment in public healthcare facilities where resources and funding are limited [1]. The economic impact of cancer extends from the financial costs of treatment, rehabilitation, end-of-life care and loss of life to the economic costs of days off work, loss of productivity, and the social-economic pressures on the family and community of cancer patients [2]. Sub-Saharan Africa has the highest HIV prevalence in the world [3]. It is a growing concern that the HIV status of a person and the antiretroviral medications increase the patients' sensitivity to toxicity from radiation therapy and chemotherapy [4–6]. There is therefore a strong need for the investigation and application of technologies which can increase cancer treatment efficacy without increasing the treatment costs in Africa. Research from The Netherlands indicates that hyperthermia technology may increase the treatment efficacy whilst lowering the healthcare costs of cervical cancer patients [7]. The investigation of the use of affordable hyperthermia technology is therefore warranted.

2. Background

Cervical cancer is classified as an AIDS defining illness by the World Health Organisation. Over 80% of the 555,000 new cervical cancer diagnoses globally per year will occur in developing countries where HIV is prevalent [8]. Cervical cancer is the second most prevalent female cancer in South Africa with around 5,000 new cases diagnosed per year. This was 16.24% of all new cancer diagnoses in 2001, the year in which the last official national cancer statistics were published [9]. Although recent statistics on cervical cancer in South Africa are lacking, doctors at the Charlotte Maxeke Johannesburg Academic hospital estimate that 20% of radiation oncology patients have cancer of the cervix, 60% of which are

Early changes in mRNA and protein expression related to cancer treatment by modulated electro-hyperthermia

Nóra Meggyesházi[1], Gábor Andócs[2], Sándor Spisák[3], and Tibor Krenács[1,4]

(1) 1st Department of Pathology and Experimental Cancer Research, Ulloi ut 26, Semmelweis University, Budapest 1085, Hungary

(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Koyama Minami, Tottori 680-8553, Tottori, Japan

(3) Molecular Medicine Research Group, Hungarian Academy of Sciences, Budapest, Hungary

(3) MTA-SE Tumor Progression Research Group, Budapest, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 249563, 3 pages
http://dx.doi.org/10.1155/2013/249563

Conference Paper

Early Changes in mRNA and Protein Expression Related to Cancer Treatment by Modulated Electrohyperthermia

Nóra Meggyesházi,[1] Gábor Andócs,[2] Sándor Spisák,[3] and Tibor Krenács[1,4]

[1] *1st Department of Pathology and Experimental Cancer Research, Ulloi ut 26, Semmelweis University, Budapest 1085, Hungary*
[2] *Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Koyama Minami, Tottori 680-8553, Tottori, Japan*
[3] *Molecular Medicine Research Group, Hungarian Academy of Sciences, Budapest, Hungary*
[4] *MTA-SE Tumor Progression Research Group, Budapest, Hungary*

Correspondence should be addressed to Tibor Krenács; krenacst@gmail.com

Received 16 January 2013; Accepted 26 May 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Nóra Meggyesházi at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Modulated electrohyperthermia (mEHT), generated by capacitive coupled, modulated 13.56 MHz radiofrequency, is a noninvasive technique for targeted tumor treatment based on elevated ion concentration and electric admittance in malignant tumors. In this study, we tested early changes in protein expression related to tumor destruction upon a single shot of 30-minute mEHT treatment of xenografted human colorectal cell line (HT29) implanted into the femoral region of Balb/c nu/nu mice. Treatment-related mRNA expression profiling was done using the human genome U133 Plus 2.0 Arrays. Apoptosis protein arrays and immunohistochemistry were performed for validating changes at the protein level. The mEHT treatment resulted in major expression changes in 48 genes including several heat-shock proteins. Apoptosis protein arrays revealed the upregulation of death receptors, Bcl-2 superfamily mitochondrial apoptosis regulatory proteins, and heat-shock proteins, which were also confirmed in situ. Within 24-hour post-treatment, mEHT resulted in the upregulation apoptosis induction and heat-shock-related gene and protein expression in HT29 colorectal cancer xenografts contributing to tumor destruction.

1. Background

Modulated electrohyperthermia (mEHT) is a wildly used noninvasive technique for targeted tumor treatment [1–4]. The capacitive coupled modulated radiofrequency enriches in the tumor tissue (because of its dielectric differences [5]) without harming the surrounding nonmalignant tissues. Beside the temperature-dependent effect mEHT causes in the tumor tissue, it has a nontemperature-dependent tumor destruction effect, which is three times higher than the conventional hyperthermia with the temperature-dependent outcome only [6]. Here our aim was to study early changes in protein expression either related or not to the temperature changes in tumors treated with a single shot of mEHT.

2. Method

HT29 human colorectal carcinoma cell line is xenografted to both femoral regions of Balb/c nu/nu mice. Tumors (approx. 1.5 cm diameter) were treated with a single-shot mEHT treatment (LabEHY, Oncotherm Ltd., Páty, Hungary) for 30 minutes. Temperature measurement was carried out during the treatment in the treated tumor core, and subcutaneously, in the opposite (treated control) tumor core and rectally. The treated tumor core temperature was between 41-42°C during the treatment. Sample was taken at 0, 1, 4, 8, 14, 24, and 48 h after the treatment with each group containing 3 mice alongside with 2 untreated control animals (sample was taken simultaneously with the 24 h treated group).

Lyme Disease and Oncothermia

Ortwin Zais[1]

(1) Hyperthermiezentrum Hochwald, Trierer Straße 44, 54411 Hermeskeil, Germany

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 275013, 3 pages
http://dx.doi.org/10.1155/2013/275013

Conference Paper

Lyme Disease and Oncothermia

Ortwin Zais

Hyperthermiezentrum Hochwald, Trierer Straße 44, 54411 Hermeskeil, Germany

Correspondence should be addressed to Ortwin Zais; o.zais@hyperthermiezentrum-hochwald.de

Received 16 January 2013; Accepted 18 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Ortwin Zais at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Lyme disease is a tick-borne disease with multiple organ failures, and systemic disorders. Dramatic change becomes apparent in the chronic phase of the disease. Chronic fatigue syndrome, lapse of concentration, depression, joint pain, and muscle pain are a few, but major clinical symptoms characterizing the disease. The human immune system is defenseless. *Borrelia* uses various mechanisms to escape from immunoattacks or antibiotic therapies. This "stealth phenomenon" needs new therapeutic principles to be interrupted. Our objective in this paper is to study the effect of oncothermia, which is a well-established oncological therapy, on Lyme disease. First, in our present work, we definitely concentrate on the quality of life of the patients.

1. Background

Lyme borreliosis (LB), or Lyme disease, is transmitted by ticks of the *Ixodes ricinus* complex. Its manifestations had been documented [1]. The etiologic agent, *Borrelia burgdorferi*, was first isolated from the vector tick *Ixodes dammini* (now *I. scapularis*) [2]. *Borrelia burgdorferi* is a bacterial species of the Spirochete class of the genus *Borrelia*, which has a double-membrane envelope [3]. *Borrelia burgdorferi* is one of the few pathogenic bacteria that can survive without iron, having replaced all of its iron-sulfur cluster enzymes with enzymes that use manganese, thus avoiding the problem many pathogenic bacteria face in acquiring iron. It takes more than 24 hours of attachment for transfer of *Borrelia burgdorferi*. Huge development was made during the past 20 years understanding *Borrelia burgdorferi* and its consequent illness. Its microbiology [4], epidemiology [5], diagnosis [6, 7], and clinical practices [8–10] are studied in detail.

Clinical symptoms of Lyme disease are serious. We are listing only some major of them as follows: fatigue syndrome, lapse of concentration, depression, joint pain, muscle pain, erythema chronicum, myocarditis, cardiomyopathy, arrhythmia, arthritis, arthralgia, meningitis, neuropathies, and facial nerve palsy.

Borrelia burgdorferi infections have been linked to non-Hodgkin lymphomas, [11]. Oncothermia, well known in cancer therapy [12], might be an adequate method for treatment of Lyme disease. The applied bioelectromagnetic energy absorption acts on the cellular membrane [13] and on its regulation [14], tuning the parameters to the membrane destruction [15]. The applied interaction radiofrequency (RF) range (RF carrier with LF modulation [16, 17]) coupled by impedance (capacitive) mode could act on the cell-membrane states of the bacteria. The huge temperature gradient on the membrane could modify the HSP structure shown by DNA array involving first of all the HSP60 and HSP70 chaperones proteins [18]. *Borrelia burgdorferi* is especially sensitive on the membrane states of these HSPs [19, 20], so the effect is expected. These experimental results on the special activity of chaperones have to be clarified in more detail in connection with the applied modulation of oncothermia [21], which also modified the HSP activity [22], in consequence it could be a useful tuning parameter for selection of the bacteria.

2. Method

In 12 patients (8 male and 4 female; mean age 55 y, [39 ÷ 76]) suffering from Lyme disease the influence of oncothermia on healing processes was examined in this pilot study. Their medical history was the cohort forming ability. Tick bite was recognized for 75% (9/12) patients and erythema migrans of

Modulation effect in oncothermia

Oliver Szasz[1], Gabor Andocs[2], and Nora Meggyeshazi[3]
(1) Department of Biotechnics, St. Istvan University, Pater K. u. 1., Godollo 2100, Hungary
(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Minami, Koyama-Cho, Tottori Prefecture 680-8553, Japan
(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Üllői út 26, Budapest 1085, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 398678, 5 pages
http://dx.doi.org/10.1155/2013/398678

Conference Paper

Modulation Effect in Oncothermia

Oliver Szasz,[1] Gabor Andocs,[2] and Nora Meggyeshazi[3]

[1] *Department of Biotechnics, St. Istvan University, Pater K. u. 1., Godollo 2100, Hungary*
[2] *Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 4-101 Minami, Koyama-Cho, Tottori Prefecture 680-8553, Japan*
[3] *1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Üllői út 26, Budapest 1085, Hungary*

Correspondence should be addressed to Oliver Szasz; droliverszasz@gmail.com

Received 15 January 2013; Accepted 9 May 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Oliver Szasz at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Conventional hyperthermia is based on the local or systemic heating, which is measured by the realized temperature in the process. Oncothermia applies nanoheating, which means high energy absorption in the nanoscopic range of the malignant cell membrane selectively. This high temperature and its consequent stress create special effects: it evolves the possibility for chaperone proteins to be expressed on the outer membrane by softening the membrane and starts various excitations for programmed cell death of the targeted malignant cell. The process needs special delivery of the energy which selects as desired. A strict 13.56 MHz sinusoidal carrier frequency is amplitude modulated by time-fractal signals. The modulation is far from any sinus or other periodic patterns; it is a 1/f spectrum having definite templates for its construction. In some personalized cases, a definite template is used for the fractal pattern, which is copied from the actual character of the tumor pathology or any other specialty of the target.

1. Introduction

To understand the principle of modulation, let us start with a simple everyday task: to listen to our favorite radiobroadcasts, like 107.1 MHz Cologne, 91.8 MHz Frankfurt, Radio Energy (Munich) 93.3 MHz, and so forth. We should choose the frequency (tune the radio to select it), and we can enjoy the broadcast. The carrier frequency which was the basis of the tuning never meets the ear; it is too high to sense, and anyway it would be a too monotonic sound as it is only a single frequency. Instead of monotony, we hear the music or other information carried by this chosen frequency. The carrier frequency delivers the real information coded in its modulation (see Figure 1).

The carrier frequency carries two important information characters:

(i) its modulation finds the target on cellular level;

(ii) its energy heats up the selected cells from the outside by its neighboring extracellular matrix.

The modulation method is similar to the process when light goes through the window's glass. When the glass is transparent to a specific set of colors (visible light, definite interval of frequencies), its absorption is almost zero; all energy goes through it. However, when it has any bubbles, grains, precipitations, and so forth, those irregularities will absorb a bigger part of the energy, their transparency will be locally low, their energy absorption will be high, and they will be heated up locally. It is a self-selection depending on the material and the frequency (color) which we apply in the given example. The carrier frequency delivers the information (modulation frequencies), for which the cancer cells are much less "transparent" than their healthy counterpart is. Malignant cells are heated up by the selectively absorbed energy.

The applied signal has synergy with the heating of the extracellular matrix, constructing zero-mode noise component which surpasses the thermal noise [1]. The "demodulation" of the noise [2] uses the ratchet mechanism [3] and the stochastic resonance phenomena [4] combined with the membrane rectification [5] and nonlinearity [6].

Report of the pilot-study done for the proposed investigation on the possible synergic effect between high dose ascorbic acid application and oncothermia treatment

Csaba Kovago[1], Nora Meggyeshazi[2], Gabor Andocs[3], and Andras Szasz[4]
(1) Pharmacology and Toxicology Department, Faculty of Veterinary Science, Szent Istvan University, Budapest 1078, Hungary
(2) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest 1085, Hungary
(3) University of Tottori, Tottori 680-8550, Japan
(3) Biotechnics Department, Faculty of Mechanical Engineering, Szent Istvan University, Gödöllő 2100, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 386913, 2 pages
http://dx.doi.org/10.1155/2013/386913

Conference Paper

Report of the Pilot Study Done for the Proposed Investigation on the Possible Synergic Effect between High-Dose Ascorbic Acid Application and Oncothermia Treatment

Csaba Kovago,[1] Nora Meggyeshazi,[2] Gabor Andocs,[3] and Andras Szasz[4]

[1] *Pharmacology and Toxicology Department, Faculty of Veterinary Science, Szent Istvan University, Budapest 1078, Hungary*
[2] *1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest 1085, Hungary*
[3] *University of Tottori, Tottori 680-8550, Japan*
[4] *Biotechnics Department, Faculty of Mechanical Engineering, Szent Istvan University, Gödöllő 2100, Hungary*

Correspondence should be addressed to Csaba Kovago; cskovago@gmail.com

Received 15 January 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Csaba Kovago at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

According to recent investigations, the parenteral application of ascorbic acid (vitamin C) at high doses has significant antitumor activity in *in vitro* assays. The goal of our experiment was to determine the possible potentiating effect of application of high dose pH-neutralized ascorbic acid to the normal oncothermia treatment method. The NMRI mice were inoculated with C26 murine colon carcinoma cell line subcutaneously at both of their femoral regions and were kept till the tumors reached symmetrically 10 mm in diameter. We created four experimental groups, containing 5 male and 5 female animals in each. Both vitamin-C and oncothermia treatments were applied once; ascorbic acid was applied *intra-peritoneally*. Oncothermia treatment was applied only to the right limb tumor; the other side will be used as internal control. After the treatment, the animals were sacrificed, and all tumors were removed and analyzed histopathologically. Our main question centers on the comparison of the cell destruction ratio of the various applied treatment regimes, and studies the possible synergy or additive cross-potentiating of the methods. The results of this experiment turned out to be controversial, since the ascorbic acid did not change the remission rate of the allografts and showed no synergy with oncothermia.

1. Introduction

According to recent investigations, the parenteral application of ascorbic acid (vitamin C) at high doses has significant antitumor activity in *in vitro* assays. This fact is very important using ascorbic acid as complementary drug with standard antitumoral therapy or in cases where currently no other potent treatment is possible. Although the beneficial effect of the ascorbic acid on antineoplastic therapy has some controversial reports in the literature [1–3] and the specific method of action is still unclear: high concentration of ascorbic acid produces oxidative shock by H_2O_2 lethal for tumor cells beyond a certain level, healthy cells can survive the same stress effect [4]. As for the application, it was reported that intravenous ascorbic acid treatment is much more efficient, since this way more than 70-fold higher plasma concentration is elucidative than in case of oral application [5]. To achieve proper effect, high plasma level of ascorbic acid is required; so in human cases intravenous dosages are considered between 0,15 and 1,5 g/kg doses [6, 7].

2. Objective

The goal of our experiment was to determine the possible potentiating effect of application of high-dose pH-neutralized ascorbic acid to the normal oncothermia treatment method. The dose we used was considered to be 2 g/kg

Low Back Pain – Complex Approach of Treatmetn by different CAM modalities (Acupunctue and other type of dry-needling, "Targeted RF non invasive Physiotherapy" for low back pain)

Hegyi Gabriella[1], and Li Jian[2]
(1) Pecs University, Health Science Faculty, CAM Department, Pet˝ofi u, 79, Budapest 1196, Hungary
(2) Hebei United University, TCM Department, Tangshan, Hebei, China

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 326595, 8 pages
http://dx.doi.org/10.1155/2013/326595

Conference Paper

Low Back Pain-Complex Approach of Treatment by Different CAM Modalities (Acupuncture and Other Types of Dry Needling, "Targeted RF Noninvasive Physiotherapy" for Low Back Pain)

Hegyi Gabriella[1] and Li Jian[2]

[1] *Pecs University, Health Science Faculty, CAM Department, Petõfi u, 79, Budapest 1196, Hungary*
[2] *Hebei United University, TCM Department, Tangshan, Hebei, China*

Correspondence should be addressed to Hegyi Gabriella; drhegyi@hu.inter.net

Received 15 January 2013; Accepted 19 May 2013

Academic Editors: G. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Hegyi Gabriella at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

For at least 2,500 years, acupuncture has been an integral part of the traditional Chinese medicine. Recently, more people are diagnosed with chronic disease, and many of them are poorly treated with conventional therapies. Those frequently prefer other forms of complementary medical treatments. Based on the theory of homeostatic equilibrium being the basis of health, acupuncture focuses on restoring the homeostasis by manipulation of the complementary and opposing elements of *yin* and *yang*. It is possible that by affecting *afferent nerve signaling*, acupuncture may influence the release of endogenous opioids to promote pain relief. Our objective is giving western trained physicians clinical applications together with acupuncture and modern physiotherapeutic equipment (*booster*) to accommodate accelerating interests in acupuncture and related techniques in modern complex treatment of chronic low back pain. In recent prospective phase I/II study, statistical data verified the relevant end points of the study: the safety, the quality of life (QoL), the rest time, duration of painless state, and cost/benefit ratio.

1. Introduction

Thirty-five RCTs covering 2861 patients were included in a systematic review [1]. There was insufficient evidence to make any recommendations about acupuncture or dry needling for acute low back pain, but for chronic low back pain, results showed that acupuncture is more effective for pain relief than no treatment or sham treatment, in measurements taken up to three months. The results also showed that for chronic low back pain, acupuncture is more effective for improving function than no treatment, in the short term [2]. Acupuncture is not more effective than other conventional and "alternative" treatments. When different types of acupuncture were added to other conventional therapies, they relieved pain and improved function better than the conventional therapies alone with less intake pharmacologic substances and side effects of them.

We were going to apply in our randomized pilot study more complementary and alternative methods (CAMs) treatments for low back pain and evaluate their effect on visual analogue scale (VAS) and quality of life (QoL) of patients [3]. CAM modalities, including "dry needling," lately improved noninvasive RF therapy appears to be a useful adjunct to other therapies for chronic low-back pain with life-style management individually developed. ("Personalized medicine").

Although chronic low-back pain is usually a self-limiting and benign disease that tends to improve spontaneously over time, a large variety of therapeutic interventions are available for its treatment. Recovery time is different at each patient depending on his/her additional physical condition. Most of the patients are older due to developed degenerative soft-tissue damage which is a growing problem in all over the world and should be treated [4].

Complete Responses after Hyperthermic Ablation by UltraSound Guided High Intensity Focused Ultrasound (USgHIFU) Plus Systemic Chemotherapy (SC) for Locally Advanced Pancreatic Cancer

Joan Vidal-Jove[1], Marta Garcia-Bernal[2], Eloi Perich[1], and Manuel Alvarez del Catillo[3]

(1) Surgical Oncology HIFU Unit, Hospital Universitari Mutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain

(2) Pediatric Department, Hospital Universitari Mutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain

(3) Medical Direction Department, Hospital UniversitariMutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 586769, 4 pages
http://dx.doi.org/10.1155/2013/586769

Conference Paper

Complete Responses after Hyperthermic Ablation by Ultrasound Guided High Intensity Focused Ultrasound Plus Systemic Chemotherapy for Locally Advanced Pancreatic Cancer

Joan Vidal-Jove,[1] Marta Garcia-Bernal,[2] Eloi Perich,[1] and Manuel Alvarez del Castillo[3]

[1] *Surgical Oncology HIFU Unit, Hospital Universitari Mutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain*
[2] *Pediatric Department, Hospital Universitari Mutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain*
[3] *Medical Direction Department, Hospital Universitari Mutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain*

Correspondence should be addressed to Joan Vidal-Jove; jvidal@mutuaterrassa.es

Received 14 January 2013; Accepted 3 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, D. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Joan Vidal-Jove at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

We describe results in unresectable pancreatic tumors treated with USgHIFU hyperthermia ablation plus adjuvant chemotherapy. *Materials and Methods.* Thirty two cases of nonresectable pancreatic tumors were treated from March 2010 to March 2012, and all of them underwent systemic chemotherapy. Clinical responses (thermal ablation achieved) were measured by image techniques. There were 23 stage III cases and 9 stage IV cases. Complications were also analyzed. *Results.* Clinical responses (ablation obtained) were 82% in all cases, sustained at 8 weeks of the procedure. We obtained 8 complete responses (25%) at the end of the combined treatment, 7 from stage III patients and 1 from stage IV. Major complications included (1) severe pancreatitis with GI bleeding and (2) skin burning grade III that required plastic surgery. No deaths were registered. Median survival was 12.5 month (6 months–2.5 year). *Conclusion.* HIFU plus SC is a potentially effective and safe modality for the treatment of unresectable pancreatic cancer.

1. Introduction

Despite continuous scientific advances in the field of oncology, pancreatic cancer has a poor prognosis nowadays. A significant part of cases is considered unresectable at diagnosis due to late detection of the disease or to invasion of great vessels surrounding the tumor [1]. Therefore, treatments with chemotherapy and in lesser grade radiotherapy are the only tools suitable to be offered to the patients with locally advanced disease [2]. Overall survival is around 6–10 months in stage III patients and only 3–6 months for stage IV cases [1].

US-guided HIFU is a feasible technique with no mortality, low morbidity, and promising results (Figure 1). At present, there are several ablation techniques employed to treat tumors in different locations. Radiofrequency, cryotherapy, ethanol injection, or embolisation are considered for tumors in several locations except pancreas tumors. At present, there is no ablative technique suitable for pancreatic lesions. High intensity focused ultrasound (HIFU) is a minimally invasive surgical technique that has proven to improve the local control in different types of tumors. Several studies in animals and humans have shown the efficacy of this technique to cause a coagulative necrosis that able to diminish or even ablate tumoral masses. Previous reports of the treatment of pancreatic masses by HIFU have been published recently, specially underlining its role as a good concomitant treatment associated to gemcitabine based chemotherapy protocols.

The HIFU Unit in Hospital Universitari Mutua Terrassa was established in 2008. First cases were exclusively uterine fibroid tumors. Since January 2010, a wide variety of malignant tumors had been treated at our institution.

Hypoxia Immunity, Metabolism and Hyperthermia

Gianfranco Baronzio[1], Mikhail Kiselevsky[2], Marco Ballerini[1], Valter Cassuti[1], Laurent Schwartz[3], Isabel Freitas[4], Giammaria Fiorentini[5], and Gurdev Parmar[6]

(1) Centro Medico Demetra, Center for Clinical Hyperthermia and Immunity, Via Staderini, 19/B, 05100 Terni, Italy
(2) Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow 115478, Russia
(3) Laboratoire d'Informatique, Ecole Polytechnique, 91128 Palaiseau, France
(4) Department of Animal Biology and CNR Institute of Molecular Genetics, Section of Histochemistry and Cytometry, University of Pavia, 27100 Pavia, Italy
(5) Oncology Unit, Azienda Ospedaliera Ospedale San Salvatore, 6112 Pesaro, Italy
(6) IntegratedHealth Clinic, 23242Mavis Avenue, Fort Langley, BC, Canada V1M2R4

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 528909, 5 pages
http://dx.doi.org/10.1155/2013/528909

Conference Paper

Hypoxia Immunity, Metabolism, and Hyperthermia

Gianfranco Baronzio,[1] Mikhail Kiselevsky,[2] Marco Ballerini,[1] Valter Cassuti,[1] Laurent Schwartz,[3] Isabel Freitas,[4] Giammaria Fiorentini,[5] and Gurdev Parmar[6]

[1] *Centro Medico Demetra, Center for Clinical Hyperthermia and Immunity, Via Staderini, 19/B, 05100 Terni, Italy*
[2] *Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow 115478, Russia*
[3] *Laboratoire d'Informatique, Ecole Polytechnique, 91128 Palaiseau, France*
[4] *Department of Animal Biology and CNR Institute of Molecular Genetics, Section of Histochemistry and Cytometry, University of Pavia, 27100 Pavia, Italy*
[5] *Oncology Unit, Azienda Ospedaliera Ospedale San Salvatore, 6112 Pesaro, Italy*
[6] *Integrated Health Clinic, 23242 Mavis Avenue, Fort Langley, BC, Canada V1M 2R4*

Correspondence should be addressed to Gianfranco Baronzio; barongf@intercom.it

Received 14 January 2013; Accepted 3 April 2013

Academic Editors: M. Jackson, D. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Gianfranco Baronzio at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Hypoxia is common in solid tumors and in many other disease states such as myocardial infarction, stroke, bone fracture, and pneumonitis. Once hypoxia has developed, the undernourished and hypoxic cells trigger signals in order to obtain new blood vessels to satisfy their increasing demands and to resolve hypoxia. The principal signal activated is an ancestral oxygen sensor, the hypoxia inducible factor (HIF). After its nuclear translocation, HIF triggers a series of mediators that recruit, into the hypoxic milieu, several immature myeloid, mesenchymal, and endothelial progenitors cells. Resident and recruited cells participate in the processes of neoangiogenesis, for resolving the hypoxia, while at the same time trigger an inflammatory reaction. The inflammatory reaction has as primary end point, the repair of the damaged area, but if an insufficient production of resolvins is produced, the inflammatory reaction becomes chronic and is unable to repair the damaged tissue. In this brief overview, we will show the differences and the similar events present in cancer, myocardial infarction, and stroke. Furthermore, the metabolic alterations produced in the tumor by hypoxia/HIF axis and the consequences on hyperthermic treatment are also discussed.

1. Introduction

The local inflammatory reaction is characterized by an initial increase in blood flow to the site of injury, by increased vascular permeability, and by an ordered influx of different effector cells, recruited from the peripheral blood and bone marrow to the site of lesion [1].

Another characteristic of the inflammatory reaction is the presence of hypoxia and its modulation of innate immunity [2].

In this overview, we will analyze the influence of the hypoxic state on inflammation and compare its interaction in diverse disease states including cancer. Interestingly, the body's response to hypoxia in different pathological situations seems to be quite similar (see Box 1).

2. Hypoxia as a Homeostatic Response

Once hypoxia has developed, the undernourished and hypoxic cells present trigger signals, in order to obtain new blood vessels, and satisfy their ever-increasing demands. The principal signal activates an ancestral oxygen sensor, the hypoxia inducible factor (HIF). HIF is a conserved mechanism of defense present in mammals, aimed at reestablishing a supply of oxygen and nutritive substances. After its nuclear translocation, HIF triggers a series of mediators such as

Autoregulation of the Brain Temperature During Whole Body Hyperthermia

Haim I. Bicher[1], Nodar Mitagvaria[2], Marina Devdariani[2], Lia Davlianidze[2], Martina Nebieridze[2], and Nana Momtselidze[2]

(1) Bicher Cancer Institute, 12099WWashington Boulevard, No. 304, Los Angeles, CA 90066, USA
(2) I. Beritashvili Center of Experimental Biomedicine, 14 Gotua Street, 0160 Tbilisi, Georgia

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 928243, 5 pages
http://dx.doi.org/10.1155/2013/928243

Conference Paper

Autoregulation of the Brain Temperature during Whole Body Hyperthermia

Haim I. Bicher,[1] Nodar Mitagvaria,[2] Marina Devdariani,[2] Lia Davlianidze,[2] Marina Nebieridze,[2] and Nana Momtselidze[2]

[1] *Bicher Cancer Institute, 12099 W Washington Boulevard, No. 304, Los Angeles, CA 90066, USA*
[2] *I. Beritashvili Center of Experimental Biomedicine, 14 Gotua Street, 0160 Tbilisi, Georgia*

Correspondence should be addressed to Nodar Mitagvaria; nodmit@gmail.com

Received 14 January 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Nodar Mitagvaria at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

The aim of this study was revealing the temperature changes in rats' brain tissue caused by whole body hyperthermia. The analysis of received results allows to conclude that the brain has a highly secured system of temperature autoregulation against the exogenous temperature changes. The upper limit of this autoregulation (for rats, at least) is in the range of 45°C of environment. An important role in the normal functioning of the brain temperature autoregulation system belongs to Nitric Oxide. The behavioral disorders, observed in animals after whole body hyperthermia (sure within the range of brain temperature autoregulation) are hardly associated with the changes in temperature of the Central Nervous System, but rather have to be mediated by impaired blood circulation and oxygen supply to the brain tissues, caused by the rapid deterioration of the blood rheological properties.

1. Introduction

In our previous experimental studies significant morpho-physiological changes in the rats' brains tissue caused by local hyperthermia (43°C, 60 min. exposure) have been revealed [1, 2]. On Figure 1 we can see the clear-cut edge of damaged tissue in the rat's cerebral cortex. Analysis of the results allowed us to conclude that in the development of these changes essential role belongs to the mechanism associated with intense activation of Nitric Oxide Synthases (NOS), resulting (in the initial phase of hyperthermic exposure) in increased oxygenation of exposed brain tissue, and then (in the second phase of exposure), to changes in blood rheological properties resulting in thrombosis of cerebral vessels [3].

Confirmation of this conclusion is presented in Figures 2(a) and 2(b). In Figure 2(a) we can see a sensory-motor cortex of rats' brains with a lot of thrombosed cerebral vessels after 60 minutes of hyperthermic exposure in control rats brains, and in Figure 2(b), the similar picture in experimental rats' brains with inhibited production of Nitric Oxide, we can see just a single thrombosed cerebral vessels.

In the case of tumor tissue, we believe that the initial thermal hyperemia leads to a deterioration in the process of glycolysis due to increased oxygenation of tissues (Pasteur effect), and subsequent thrombosis leads to the sharp decrease in glucose delivery to tumor cells and to their unconditional death. Based on the foregoing, we attempted to evaluate the possible role of these phenomena in behavioral disturbances in rats observed after whole body hyperthermia [4]. For this purpose, we implanted specially made thermocouples in the subcortical structures of the rats' brains, which allowed us to record changes in temperature of the brain tissue at different temperatures in HC.

Two series of experiments have been carried out—on intact animals and on animals with previously administered

Hyperthermia versus Oncothermia: Cellular effects in cancer therapy

Gyula P. Szigeti[1,2], Gabriella Hegyi[3], and Olivér Szasz[4]
(1) Department of Physiology, University of Debrecen, Debrecen 4012, Hungary
(2) Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest 1094, Hungary
(3) Department of Complementary and Alternative Medicine, University of Pécs, Pécs 7622, Hungary
(4) Department of Biotechnics, St. Istvan University, Gödöllő 2103, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 274687, 4 pages
http://dx.doi.org/10.1155/2013/274687

Conference Paper

Hyperthermia versus Oncothermia: Cellular Effects in Cancer Therapy

Gyula P. Szigeti,[1,2] Gabriella Hegyi,[3] and Olivér Szasz[4]

[1] *Department of Physiology, University of Debrecen, Debrecen 4012, Hungary*
[2] *Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest 1094, Hungary*
[3] *Department of Complementary and Alternative Medicine, University of Pécs, Pécs 7622, Hungary*
[4] *Department of Biotechnics, St. Istvan University, Gödöllő 2103, Hungary*

Correspondence should be addressed to Gyula P. Szigeti; szigeti.gyulapeter@gmail.com

Received 14 January 2013; Accepted 29 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Gyula P. Szigeti at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Hyperthermia means overheating of the living object completely or partly. Hyperthermia, the procedure of raising the temperature of a part of or the whole body above the normal for a defined period of time, is applied alone or as an adjunctive with various established cancer treatment modalities such as radiotherapy and chemotherapy. The fact that is the hyperthermia is not generally accepted as conventional therapy. The problem is its controversial performance. The controversy is originated from the complications of the deep heating and the focusing of the heat effect. The idea of *oncothermia* solves the selective deep action on nearly cellular resolution. We would like to demonstrate the force and perspectives of oncothermia as a highly specialized hyperthermia in clinical oncology. Our aim is to prove the ability of oncothermia to be a candidate to become a widely accepted modality of the standard cancer care. We would like to show the proofs and the challenges of the hyperthermia and oncothermia applications to provide the presently available data and summarize the knowledge in the topic. Like many early-stage therapies, oncothermia lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications.

1. Introduction

In oncology, the term "hyperthermia" refers to the treatment of malignant diseases by administering heat in various ways. Hyperthermia is usually applied as an adjunct to an already established treatment modality, where tumor temperatures in the range of 40–46°C are aspired. Interstitial hyperthermia and whole-body hyperthermia are still under clinical investigation, and a few positive comparative trials have already been completed. Parallel to clinical research, several aspects of heat action have been examined in numerous preclinical studies [1–3].

The traditional *hyperthermia* is controlled the only single thermodynamic intensive parameter, with the temperature. *Oncothermia*, which is a "spin-off" form of the hyperthermia, is based on the paradigm of the energy dose control, replacing the single temperature concept [4]. With this approach, oncothermia returned to the gold standards of the dose concepts in medicine: instead of the parameter, which cannot be regarded as dose (the temperature does not depend on the volume or mass), oncothermia uses the energy (kJ/kg [=Gy]), like the radiation oncology uses the same (Gy) to characterize the dosing of the treatment [5].

2. The Concept of Hyperthermia

The effectiveness of hyperthermia treatment is related to the temperature achieved during the treatment, as well as the length of treatment and cell and tissue characteristics. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumor and surrounding

Burden of oncothermia – Why is it special?

Oliver Szasz[1,2]
(1) Department of Biotechnics, St. Istvan University, 2100 Godollo, Pater K. u. 1., 2100-Godollo, Hungary
(2) Oncotherm GmbH, Belgische Allee 9, 53842 Troisdorf, Germany

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 938689, 6 pages
http://dx.doi.org/10.1155/2013/938689

Conference Paper

Burden of Oncothermia: Why Is It Special?

Oliver Szasz[1,2]

[1] *Department of Biotechnics, St. Istvan University, 2100 Godollo, Pater K. u. 1., 2100-Godollo, Hungary*
[2] *Oncotherm GmbH, Belgische Allee 9, 53842 Troisdorf, Germany*

Correspondence should be addressed to Oliver Szasz; droliverszasz@gmail.com

Received 11 January 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, D. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Oliver Szasz at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

There are many contradictory opinions about conventional hyperthermia in oncology. The main points are the physical and technical imperfection of classical heating, as well as the limits of the natural physiological feedback of the organism. We would like to present the definitive differences between oncothermia and conventional hyperthermia, explaining the new line of problem solving in this important field of oncology.

1. Problem

The general opinion among specialists is that the physics limits the deep heating [1]. The limit is formed by the heat conduction and other thermodynamic factors. The imperfect thermal conditions are combined with insufficient electrodynamic facilities to concentrate the energy focused in depth. This inadequacy appears in the unwanted hot spots and the overheated surface when the actually necessary energy is pumped through.

Some experts evaluated the situation a bit differently, blaming the biophysical, physiological factors having technical inefficiencies. According to this position, the physiological negative feedback seeking to reestablish the thermal homeostasis block its proper job, [2].

Certainly, both the physical and physiological deficiencies are involved in the hindrance of the success and probably it is accompanied with a factor of improper references too. In case of comparison of various heating methods, the only factor measured as relevant is the temperature in the targeted volume. However, this reference has various complex shortages and could lead to misleading consequences. The high temperature ablation in a small volume for short time cannot be compared with a longer time local or regional heating or it is even less comparable with the whole body heating on the same temperature. When the local or regional heating reaches 41.5°C homogeneously in the target that could be a therapeutic indicator of success. However, in case of whole body hyperthermia the same homogeneous temperature could be reached, but no more curative effect is observed, it does not give the final solution of heat-therapy. Moreover, the results are completely different from the expectations of a therapist trained in local heating methods. The temperature alone is not a reference point [3], because the physiological conditions modify the actual state even when the temperature is equal. Typical example is the difference of the blood heating approaches and tissue heating ones. In blood heating cases (e.g., limb perfusion, subcutane radiative heating), the hot blood heats up the tumor. In case of the tissue, heating the blood remains cold (stays on body temperature). This difference makes huge deviations in the thermal and physiological actions: in the first case, the heat flows from the blood to the target, while in the second case it is completely the opposite. In the first case the static thermal equilibrium can be reached after a definite time, while in the second case the thermal equilibrium always remains dynamic; the heat-flow is always active from the heated volume to the other body parts by the blood flow. In this second case, the heated volume (tumor) is a hot heat source to heat the body up.

Androtherm Application for "La Peyronie" Disease

M. Ballerini[1], G.F. Baronzio[1], G. Capitó[1], O. Szasz[2], and V. Cassutti[1]
(1) Centro Medico Demetra, Via Staderini 19, 05100 Terni, Italy
(2) Department of Biotechnics, St Istvan University, Pater K. u. 1., Gödöllő 2100, Hungary

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 962349, 6 pages
http://dx.doi.org/10.1155/2013/962349

Conference Paper

Androtherm Application for the Peyronie's Disease

M. Ballerini,[1] G. F. Baronzio,[1] G. Capitò,[1] O. Szasz,[2] and V. Cassutti[1]

[1] *Centro Medico Demetra, Via Staderini 19, 05100 Terni, Italy*
[2] *Department of Biotechnics, St Istvan University, Pater K. u. 1., Gödöllö 2100, Hungary*

Correspondence should be addressed to V. Cassutti; casvalt@libero.it

Received 11 January 2013; Accepted 4 April 2013

Academic Editors: M. Jackson and A. Szasz

This Conference Paper is based on a presentation given by M. Ballerini at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Peyronie's disease is characterized by a scarring fibrosis within the tunica albuginea of the penis that could lead to penile length loss, narrowing, curvature, erectile dysfunction, or pain with erection. This problem has recently no appropriate treatment. Our objective is to treat this kind of disease by a new kind of hyperthermia method.

1. Introduction

1.1. Prevalence. The Peyronie's disease (induratio penis plastic) is a developmental condition with acquired fibrotic changes and development of a fibrous plaque (fibrous inelastic scar) on the tunica albuginea of the penis. The Peyronie's disease is mostly observable at men in their middle ages (50–60 years) in Caucasian race [1]. The prevalence, commonly reported, is about 3%–9% [2], but according to the autopsy statistics the disease would be present in more than 20% of men [3]. It can also be an asymptomatic finding in almost 4% of male population seeking medical attention [4, 5]. In general the men, aged 40–60, are affected by Peyronie's disease in 2%-3% [6].

Actually we think that shame, fear, and poor possibilities of healing [7] are the main causes of reduced demand for medical consultation, although it also causes unpleasant side effects such as not agreeing to the modifications of the penis, reduction of self-esteem, impaired job performances, increased interpersonal conflicts, and depression.

Now, thanks to the many sources of information, the patient is aware of the limited possibilities of therapy and knows perfectly well that there is little chance of spontaneous recovery (15% of second Mulhall) [8].

1.2. Pathophysiology. Relatively little is known about the source of the disease, but nowadays there is growing consensus on the possibility of an external stress received, most likely in the erect state, during sexual intercourse or masturbation.

Trauma during sexual activity can occur for several reasons: vehement and prolonged masturbation, instinctive and sudden movement of the penis, accidental contrast of the penis against the female perineum, difficulty in penetration due to lack of lubrication of the vagina, and lack of penile erection.

The abrupt penis deformation during sexual intercourse may disrupt small vessels within the tunica albuginea with blood trapped between the layers of the tunica.

The hematoma is responsible for excessive release of cytokines, of transforming growth factor (TGF beta1), as a reaction to an autoimmune response. It is followed by an overproduction of collagen, high production of extracellular matrix, accumulation of fibroblasts and myofibroblasts, and decrease of elastic fibers [9].

This process, characterized by an abnormal healing of hematoma with the occurrence of scar, implies the coexistence of an autoimmune process probably leading to a genetic factor.

In 75% of patients affected by Peyronie's disease, high levels of antielastin antibodies [10] and a higher incidence of histocompatibility antigens HLA-27 are shown [11]. The autoimmune reaction may have, in some individuals, a certain degree of genetic predisposition.

Electrochemical Therapy of Tumors

Li Jing-Hong[1] and Xin Yu Ling[1]
(1) China-Japan Friendship Hospital, Ministry of Health, Beijing 100029, China

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 858319, 13 pages
http://dx.doi.org/10.1155/2013/858319

Conference Paper

Electrochemical Therapy of Tumors

Li Jing-Hong and Xin Yu Ling

China-Japan Friendship Hospital, Ministry of Health, Beijing 100029, China

Correspondence should be addressed to Li Jing-Hong; ljinghong@gmail.com

Received 15 February 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Li Jing-Hong at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Application of electric current for the tumor destruction has a long time history. The theory of the direct galvanic current (galvanotherapy, GT) is worked out by B. Nordenstrom in the frame of biologically closed electric circuits (BCECs). Later, GT was extended by chemical considerations (EChT), and, starting with pioneering work of Professor Xin Yu Ling, a wide, intensive application had been developed in China. My objective is showing the principles and practice of the EChT treatment modality for multiple advanced lesions.

1. Introduction

The efficacy of electrochemical therapy (EChT) in mice with implanted Jensen sarcoma tumors was reported in 1953 by Reis and Henninger [1]. However, the clinical application of this modality was initiated by the Swedish radiologist, Nordenstrom. In 1983, he published a book in which he described his theory of biologically closed electrical circuits (BCECs) and the results of two decades of research on EChT treatment of malignancies in animals based on this [2]. He also reported the results of EChT in 20 lung cancer patients with 26 tumors in which he used the "skinny needle" he had developed for biopsy purposes as an electrode. Followup after 2 to 5 years revealed that 12 tumors had either disappeared or were markedly reduced in size. This study stimulated interest in utilizing EChT for treating lung malignancies, and Japanese researchers subsequently confirmed Nordenstrom's results in animals and in several patients [3–7].

Anyway, the real application of the technique widely has begun in China (China-Japan Friendship Hospital as the center of this application) after it was introduced to the country in 1987. Electrodes, which special produced by platinum, were inserted into tumor and connecting them with an apparatus, the current arouse strong chemical reactions around electrodes and led degeneration and necrosis of tumor cells. It is a new type method to treat tumor without surgical resection. The final result is caused by current inducing chemical reactions, so we call it EChT.

The advantages of EChT are that it is much safer, easier to administer, less costly than surgical procedures, and can be just as effective in certain instances. In addition, it provides an opportunity to treat tumors in those patients in whom surgery, radiation, and/or chemotherapy has not been successful or may be contraindicated.

2. Experimental Studies on Mechanism of EChT

It has been well established that tumor cells are more sensitive to certain changes in the environment than adjacent normal cells. Various treatment approaches, including radiation, chemotherapy, hyperthermia, microwave, laser, and antiangiogenesis strategies, are based on these differences.

Multiple pathological changes occur in the tumor tissue during EChT such as pyknosis of nuclei, disruption of cell membranes, disappearance of mitochondria, as well as coagulation and necrosis of nuclear proteins [2].

In animal experiments, histopathological studies have demonstrated that the killing effect of EChT on tumor tissue

The History of Hyperthermia Rise and Decline

Sergey Roussakow[1]
(1) Galenic Research Institute, Moscow, Russia

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 428027, 40 pages
http://dx.doi.org/10.1155/2013/428027

Conference Paper

The History of Hyperthermia Rise and Decline

Sergey Roussakow

Galenic Research Institute, Moscow, Russia

Correspondence should be addressed to Sergey Roussakow; roussakow@gmail.com

Received 13 February 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Sergey Roussakow at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

Electromagnetic hyperthermia remains experimental treatment after 40 years of research and application in view of its "temperature concept" based on the belief that temperature is the only parameter of the efficacy. Initial "extreme hyperthermia" concept was based on the wrong premise of much higher thermal susceptibility of malignant cells and broad therapeutic range of hyperthermia, allowing to kill tumor cells by above-threshold (>43°C) temperature without damaging healthy tissues. Indeed, this therapeutic gap is minor or absent which makes the extreme hyperthermia impossible. The next concept of "thermal dose" was based on the ungrounded extrapolation of the biochemical Arrhenius relationship onto the living matter and formed the basis of "moderate hyperthermia" concept, believing that it could enhance tumor oxygenation and radio- and chemosensitivity, ignoring the special features of tumor blood flow. Both concepts have not been confirmed; "thermal dose" is currently proven to be not connected with any clinical outcome. Analysis of randomized trials with respect to biases has not confirmed hyperthermia efficacy. The growing evidence of athermal effects and their broad application has caused development of some athermal cancer treatments. Hyperthermia concept should be cardinally reevaluated now with respect to obvious bankruptcy of the temperature concept and development of the athermal concept.

"Those who cannot remember the past are condemned to repeat it"
George Santayana, *"Life of Reason I"*
"The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact"
Thomas Henry Huxley

1. Introduction

The treatment of any problem begins from the recognition of the problem. "I'm John, I'm alcoholic"—this is the start of a return. There is no any hope for cure without this recognition. Hyperthermia is in crisis already for two decades, but still there is no awareness of the problem. This is the main reason, why hyperthermia in its current state cannot be cured.

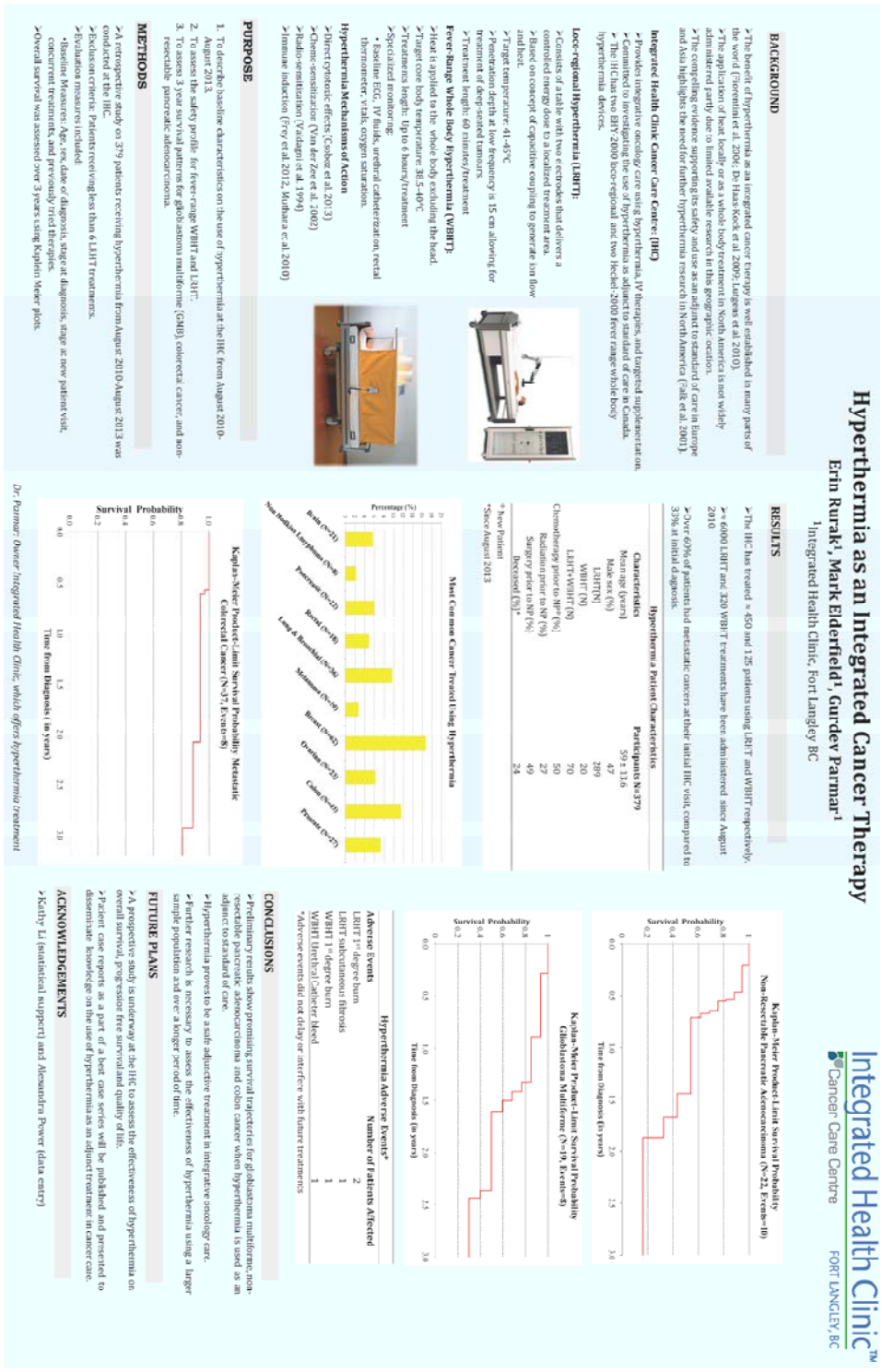
First, we have to state unequivocally: "Hyperthermia is in deep crisis." Only a blind does not see it. If we remember how many top class US medical research centers were active in hyperthermia field 20–30 years ago and how many of them show residual activity now, the conclusion is obvious. After 50 years of intensive development, having more clinical trials and publications than any modern popular pharmaceutical, hyperthermia is not accepted in any branch of oncology. One-two occasional inclusion in one-two guidelines as "the last hope therapy" with many controversies is the demonstrative result of this development.

Such a pity situation necessarily should have objective reasons. It is not enough to claim for lack of money, competition with radiology and chemotherapy, and so on. Our recent analysis of hyperthermia randomized trials [1] clearly showed the real reason of the situation: the lack of real clinical

Scientific Oncothermia poster from Canada

Hyperthermia as an Integrated Cancer Therapy

Erin Rurak[1], Mark Elderfield[1], Gurdev Parmar[1]
(1) Integrated Health Clinic, Fort Langley BC



Scientific Oncothermia poster from Canada / Wissenschaftliches Oncothermie Poster aus Kanada

In September of 2013 Integrated Health Clinic (IHC) Cancer Care Centre launched a retrospective study to assess the impact of introducing integrative therapies into a cancer patient's personalized treatment plan. Our Project Investigators compiled the data collected over the past three years at Integrated Health Clinic Cancer Care Centre, and provided that data to a third party to conduct a statistical analysis. This retrospective analysis was aimed at providing the first in-Canada clinical evaluation of the adjunctive use of Loco-Regional Hyperthermia (LRHT) and it's impact to Overall Survival (OS).

Specifically, the stated purpose was:

- To describe baseline characteristics on the use of hyperthermia at the IHC from August 2010-August 2013.
- To assess the safety profile for fever-range Whole Body Hyperthermia (WBHT) and LRHT.
- To assess 3 year survival patterns for glioblastoma multiforme (GMB), colorectal cancer, and non-resectable pancreatic adenocarcinoma.

The resulting research poster was presented at the Society for Integrative Oncology conference held at the Fairmont Vancouver in October, 2013, and again at the Oncology Association of Naturopathic Physicians conference in Phoenix this past February.
Preliminary results show promising survival trajectories for glioblastoma multiforme, non-resectable pancreatic adenocarcinoma and colon cancer when hyperthermia is used as an adjunct to standard of care therapies. In addition, hyperthermia proves to be a safe adjunctive treatment in integrative oncology care.

Further research is necessary to assess the effectiveness of hyperthermia using a larger sample population and over a longer period of time. Consequently, we are preparing to continue our research efforts and are developing a prospective data collection project on the adjunctive use of both LRHT and WBHT. Prospectively, we are aiming to provide further clinical data including Quality of Life (QOL) and Progression Free Survival (PFS). (in addition to Overall Survival (OS)

Im September 2013 rief das Integrated Health Clinic (ICH) Cancer Care Centre eine restrospektive Studie ins Leben, um die Wirkung von integrativen Therapien im personalisierten Behandlungsplan von Patienten zu untersuchen. Unsere Projektforscher haben die Daten der letzten drei Jahre am Integrated Health Clinic Cancer Care Centre zusammengetragen und von einer unabhängigen Stelle eine statistische Analyse erstellen lassen. Diese retrospektive Analyse sollte die erste Evaluation der kombinierten Anwendung von lokoregionaler Hyperthermie (LRHT) und ihrer Auswirkung auf die Gesamtüberlebenszeit in Kanada sein.

Im Einzelnen gab es folgende Ziele:

- Die Grundlinien der Charakteristik für die Anwendung von Hyperthermie in der ICH von August 2010-August 2013 beschreiben
- Ein Sicherheitsprofil festlegen für die Ganzkörperhyperthermie (WBHT) und die LRHT
- Ein Muster für die 3-Jahres-Überlebensrate beim Glioblastom (GMB), kolorektalen Tumoren und beim nicht-operablen pankreatischem Adenokarzinom festsetzen

Das wissenschaftliche Poster der Ergebnisse wurde bei der Konferenz der Society for Integrative Oncology im Fairmont Hotel, Vancouver im Oktober 2013 und dann noch einmal bei der Konferenz der Oncology Association of NeuropathicPhysicians im letzten Februar präsentiert.
Die vorläufigen Ergebnisse zeigen vielversprechende Überlebenskurven beim Glioblastom, nicht operablen Adenokarzinom und Darmkrebs wenn Hyperthermie parallel zu den Standardtherapien angewandt wird. Zusätzlich wird bewiesen, dass die Hyperthermie eine sichere begleitende Therapieform in der integrativen Onkologie darstellt.

Weitere Forschung mit einer größeren Gruppe sowie über einen längeren Zeitraum ist nötig um die Effektivität der Hyperthermie zu bewerten. Darum möchten wir unsere Forschungsbemühungen fortsetzen und entwickeln ein Projekt zur prospektiven Datensammlung über die begleitende Therapie sowohl mit LRHT sowie auch mit WBHT. Für die Zukunft planen wir ebenfalls die Erhebung klinischer Daten über die Lebensqualität (QOL) und das progressionsfreie Überleben (PFS). (zusätzlich zur Gesamtüberlebensrate (OS).

Advertisement

Port Moody Health
Integrative Medicine & Cancer Care
202-101 Klahanie Drive
Port Moody, BC V3H0C3, Canada
Tel.: +1 604-949-0077 – Fax: +1 604-949-0017
www.portmoodyhealth.com – info@portmoodyhealth.com

Port Moody Health Integrative Medicine & Cancer Care

Port Moody, Canada

Port Moody Health - Integrative Medicine & Cancer Care Centre, was founded by naturopathic physician, Dr. Sharon Gurm. With a vision to establish a world-class health care centre, Dr. Gurm and her team of expert health care professionals work collaboratively to deliver the most advanced and comprehensive integrative medicine for patients.

Dr. Gurm and her team believe the essence of true healing is in treating the whole person with a personalized treatment approach utilizing evidence and science-informed therapies. The clinic is situated in the beautiful, scenic oceanside community of Port Moody, 30 minutes from the City of Vancouver. The clinic treats patients from areas local, regional and abroad, seeking the exceptional service and transformative health care Port Moody Health has become known to provide - for cancer as well as a multitude of other ailments.

The growing team of integrated health care practitioners at Port Moody Health includes naturopathic physicians, international medical doctors, a doctor of traditional chinese medicine and oncology (China), nurses, acupuncturists, an ultrasound technician, a radiologist, colon hydrotherapists, a nutritionist, physician assistants and patient care coordinators.

Port Moody Health is one of the only fully integrated cancer treatment centres in Western Canada and one of just a few cancer centers in North America to offer Hyperthermia with the EHY-2000 plus device from Oncotherm. Now, North Americans no longer have to travel overseas to receive the most advanced, integrated approach for cancer treatment.

The medical director and expert cancer care physician, Dr. Sharon Gurm BSc (Genetics), ND (Board-Certified Naturopathic Physician) uses Oncothermia in conjunction with other evidence-based therapies that, when integrated strategically, deliver the most optimal outcomes for her patients.

As a physician, speaker, educator and researcher, Dr. Gurm is an expert in the field of integrative oncology. In private practice she has a clinical focus on integrative cancer care, autoimmune disorders, chronic diseases, hormone imbalance and chronic pain. Dr. Gurm is dedicated to the pursuit of excellence in whole-person integrative health care.

Port Moody Health offers a variety of treatments, therapies and advanced diagnostics to address everything from allergies to cancer. On their website (www.portmoodyheatlh.com), interested persons can not only find further information about the clinic and the details of all possible treatments, but also educational materials including professional and public lectures by Dr. Gurm. You will also find many testimonials from patients, speaking to the success of Port Moody Health - a global leader in advanced integrative medicine and cancer care.

Dar Al-Shifa Tumor Treatment Center
Jabal Amman - Ibn Khaldoun St.
Maggi Medical Center , Building No. 19
P.O. box 830086 Amman 11183 ,Jordan
Tel : +962 6 465 4803 - Fax: +962 6 465 4804
www.dar-alshifa.com - info@dar-alshifa.com

Dar Al-Shifa Tumor Treatment Center

Amman, Jordan

The DAR AL-SHIFA TUMOR TREATMENT CENTER is located in the heart of the main medical district of Jordan and considered to be the first of its kind in the region treating cancer patients by utilizing a great variety of innovative therapeutic means. The hospital offers integrative medical procedures and combinies both conventional and complementary medical techniques. With this range they provide therapy methods at the international top level. Offering this high quality level of medical therapy means improving the patients' quality of life, preventing them from suffering and side-effects.

The clinic also offers Oncothermia, a complementary medical therapy in the fight against cancer. The doctors foster holistic and patient centered approaches. They do not believe in the common saying of a one-size-suits-all method to cancer treatments, Dar al Shifa Center believes that each patient needs a unique treatment plan. Each medical is considered on its merits by them and Oncothermia perfectly matches this approach.

The center's objectives :

The Dar Al Shifa centers goal is to be the leading cancer center in the region, reaching regional and national cancer patients through advanced programs in cancer treatment, diagnosis and palliative care.

To be the recognized leader in holistic and patient-centered approach they are providing an integrative therapeutic medicine, delivered in an individualized and well-rounded approach to healthcare, with compassion at the core.

Be recognized for clinical excellence and innovation, they develop a highly coordinated patient experience, are distinguished by the quality of their people and providing fully integrated programs and services.

phytoVital • shop

Bezeichnung	Preis €	Menge
Hericium Vitalpilz Kapseln 128 St. (Monatspkg.)	59,00	
Reishi Vitalpilz Kapseln 128 St. (Monatspkg.)	59,00	
Maitake Vitalpilz Kapseln 128 St. (Monatspkg.)	59,00	
Shiitake Vitalpilz Kapseln 128 St. (Monatspkg.)	59,00	
Agaricus 300 mg Extraktkapseln 60 St. (Monatspackung)	36,00	
Cordyceps 300 mg Extraktkapseln 60 St. (Monatspackung)	36,00	
Coriolus 300 mg Extraktkapseln 60 St. (Monatspackung)	36,00	
Coprinus 500 mg Pulvertabletten 120 St. (Monatspackung)	32,00	
Polyporus 500 mg Pulvertabletten 120 St. Monatspackung)	32,00	
Auricularia 500 mg Pulvertabletten 120 St. (Monatspackung)	32,00	
Roter Imperial Ginseng 30 ST.	87,00	
Roter Ginseng Kapseln 100 ST.	59,00	
Boscari Afrikanischer Weihrauch 100 Kaps	41,80	
Weihrauch Balsam 50ml Salbe	29,90	
Ferulith 90g 180 Kapseln	39,90	
Viathen T 90 Lutschtabletten	39,90	
TNFdirekt 90 Kapseln	49,90	
ClutaCell 60 Kaps	47,80	
Oxy-Transfer 90 Lutschtabletten	37,50	
CurcumaPlus 90Kaps	22,95	
Colo FloraSan 350g Pulver	36,90	
Age PhytoHorm 90 Kaps.	37,90	
BAODERM ® Skin Relax Creme 50ml	29,95	
BAODERM ® Skin Relax Tonic 200ml	24,95	
BioKat Q10 Vitum 90 Kaps.	42,90	
C-Esther ImmunVital 90 Kaps.	33,90	
Chlorella BioClearing 90 Kaps.	34,95	
DreiBe VitFundus 90 Kaps.	38,95	
Folsäure Zytolith Vitum 90 Kaps.	38,95	
GingiSan 90 Kaps.	38,95	
IutAmin VitaPsych 90 Kaps.	38,95	
Gluco RegulatFormula 90 Kaps.	39,95	
Guarana 90 Kaps.	39.95	
HormoPhyt Femme 90 Kaps.	39.95	
InSpe-Fundus Mutter 90 Kaps.	39.95	
Kinetik Fundus 90 Kaps.	36,90	
Kid's Schulfundus Mineral 90 Kaps.	32.20	
LevoCartinin VitaBasis 90 Kaps.	38.95	
Magnesium VitaPhys 90 Kaps.	34,90	

Bezeichnung	Preis €	Menge
Omega AgePronat 90 Kaps.	38,95	
Omega Cerebral 90 Kaps.	39,95	
OsteoVitum Femme 90 Kaps.	34,95	
pH ClearingKur 300g Pulver	29,95	
pH-Nivellat Osmo 90 Kaps.	29,95	
Senior WildYams 90 Kaps.	29,95	
SojaPretect Femme 90 Kaps.	49,95	
UroHomme 90 Kaps.	44,50	
VitaminFundus Lady 90 Kaps.	34,95	
ZinkPlus KoFaktum 90 Kaps.	29,95	
ArthroKin Prävit 90 Kaps	39,50	
HyaZell 60 Kaps.	48,95	
Ortho K 30 Zellkur Liquid 30 Trinkampullen	249,00	
ArthroComb Frischzellen **14 weitere Produkte**	77,50	
Frequenztherapie 67 Produkte	34,50	
MOXA Pflaster	14,95	
Xarita 5 Gel Kaps.	49,50	
CholesterinCHECk 1 Bluttest	29,95	
GlutenCHECK 1 Test	29,95	
Schwangerschaftstest 1 Test Graviquick	8,95	
Menopausetest Memoquick 1 Test	21,95	
Ovulationstest Ovuquick 5 Test	24,95	
Vaginalpilztest Vagiquick 1 Test	26,95	
Spermientest Mann 1 Test	49,95	
Tiere		
Fell-& Hautpflege Spray für Hunde und Katzen	29,90	
ACTIVEED 60g Futterzusatz Kleintiere	34,90	
ACTIVEED 450g Futterzusatz Pferde	168,00	

Name, Vorname	
Straße	
PLZ, Ort	
Telefon	
E-Mail	
Unterschrift	

New Hope
Integrative Cancer Center
New-Hope Clinic/Tel-Aviv

Registration, Hotel reservation and abstract submission Save the dates

Welcome to Tel-Aviv, Israel!

Dr. Joseph Brenner and the "New-Hope" clinic in Tel-Aviv are honored to invite you to the: **JOINT MEETING OF THE**

33rd ANNUAL CONFERENCE OF THE INTERNATIONAL CLINICAL HYPERTHERMIA SOCIETY (ICHS)

AND THE

INTERNATIONAL ONCOTHERMIA SYMPOSIUM

The meetings will take place on November 30th-December 1st 2014 at the Tel-Aviv Dan-Panorama Hotel.

Program:

November 30th: 8:00-9:00: On-site registration
9:00-17:00 conference (including lunch and coffee breaks)
18:00-21:00 guided tour in Jaffa
21:00 Dinner at an Israeli food restaurant

December 1st: 9:00-18:00 conference (including lunch and coffee breaks)

Conference language: English
For groups bigger than 15, simultaneous translations to any language is possible.

Registration:

Registration fee: 500 Euro
Early birds registration: 425 Euro (until October 15th 2014)
Registration includes: 2 days conference
lunches and coffee brakes
Medical exhibition
Conference booklet
An evening tour to Jaffa
A dinner at an Israeli food restaurant (spouse add 40 Euro)
Registration form: at the end

Hotel Registration:

The conference hotel is the Tel-Aviv Dan-Panorama Hotel, a 5 star hotel on the beach of Tel-Aviv, walking distance from Jaffa on one side and from the main entertainment section of Tel-Aviv from the other side and 5 minutes' walk from "The Station" a famous entertainment and shopping center.

Special conference hotel fees: (Fees include breakfast and free lounge)
Deluxe and New-Deluxe rooms: Single=210 $, double=250 $
Executive room: single=258 $, double=298 $
Special rates available until October 30th 2014

Hotel registration with the special conference rates:
http://secure1.danhotels.com/danConventions

Convention Number: 1050
Convention Code: medlh
Password: med0214

Abstract submission:

Deadline is September 30th 2014.
Abstract will be submitted for oral presentation or as a poster.
Priority will be given for abstracts in the following subjects:
Hyperthermia treatment results by site (brain, pancreas etc.)
The combined effect of hyperthermia with chemo, RT and other anti-cancer treatment methods, and hyperthermia technics and protocols.
Abstracts will be published in an abstract booklet.

Send abstracts to: new-hope@zahav.net.il

Exhibition:

Manufactures of hyperthermia and other medical devices will exhibit in the hall of the conference during the 2 days conference.

About Tel-Aviv:

Tel-Aviv is the business center of Israel. It is one of the most active towns in the world with a lot of theaters, the home of the famous Israeli philharmonic orchestra, dance shows, a lot of night clubs, bars and restaurants, many shopping centers and more.

The center of the city was built in the 1930th by architect from the German Bauhouse movement. They are restored now forming one of the most spectacular cities in the world.

Dr. Joseph Brenner:

Deputy Head of Oncology, Wolfson Hospital, Holon, Israel

Chairman of New-Hope medical Center for hyperthermia and integrative cancer treatments

President of the International Clinical Hyperthermia Society (ICHS)

Contact Information:

If you have any question about the conference please write to: new-hope@zahav.net.il

or to conference secretariat: Mrs. Janina Leckler: leckler@oncotherm.de

REGISTRATION FORM

Registration payment can be done by e-mail or by money transfer.
On-site registration will be possible at the conference.
Payment is by Euro or by Israeli Shekel.

Name	
Degree (M.D, Prof, PhD, other)	
Address	
Institute	
Tel	
Fax	
Mail	
Payment: 425 Euro until October 15th, 500 Euro after this date, per person.	Amount:
Payment for accompanying persons for the Israeli dinner = 40 Euro per person	Amount:
Paid by money transfer (address below)	Amount:
Paid by credit card	Amount: Card name: Card No.: Expiry date: 3 digit number on the back (CVC number):
Date	
Signature	

Money Transfer

Account name: Medibit Lev-Hakikar 1989 Ltd.
Bank name: Israel Discount Bank
Swift code: IDBLILIT152
Clearing code: IL780111520000000607001

Medibit Lev-Hakikar 1989 Ltd.
62 Heh-Iyar St., Tel-Aviv, Israel

Israel Discount Bank Ltd.
Branch: Kikar-Hamedina
66 Heh-Iyar St.. Tel-Aviv, Israel

NEW DEVELOPMENTS

We are happy to introduce to you three new Oncotherm-developments for the optimised treatment with our devices.

The **memory foam pillow**

Is especially made for the conduction of RF-like extension of the waterbed.

Price: 148,75 €

The **temperature measurement device**

is for measuring the surface temperature for treatment and safety control.

Price: 1.190,00 €

The **phantom**

is for daily inspection and verification in the study-places.

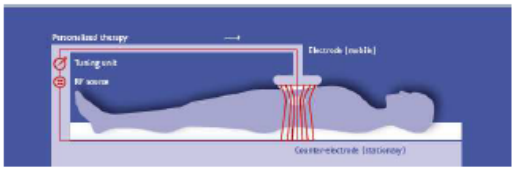
Price: 2.975,00 €

The delivery time is about 4 weeks.

You can order the devices as usual from our German office:

Tel.: +49 2241 31992 0, Fax: +49 2241 31992 11, Email: info@oncotherm.de

Information
Oncothermia-Method & Oncotherm-Devices



Oncothermia is based on the classical method of Hyperthermia, one of the oldest cancer treatment methods. Unlike conventional Hyperthermia, Oncothermia does more than simply warm up deep layers of tissue. It combines such warming with a modulated electrid field, with a carrier frequency of 13,56 MHz, that is generated by two active electrodes.

EHY-3000 series

The EHY-3000 series is designed for the simultaneous multi-local treatment of advanced, metastatic disseminated, malignant and solid tumors. Within the range of Oncothermia systems, it is the pioneering breakthrough in the fi eld of multi-local tumor therapy. Due to its highly flexible application electrodes (textile electrodes), almost all tumor locations can be treated.

EHY-2000 series

The EHY-2000 series, including EHY-2000 plus and EHY-2010, is the classic system for locoregional deep Hyperthermia applications. This series has been used for treatment throughout the world for more than 20 years. The EHY-2010 has been specially developed for practices and hospitals that have little available space but do not want to do without the classic treatment

EHY-1000 series

The EHY-1000 series is our newest development in the treatment of prostate diseases. Both malignant and benign tumors (BPH) can be treated using a catheter system with built-in electrode and counter electrode.

Booster

The Booster is a product innovation in the field of complementary treatments. Its use enhances the effects of drug treatment and it can be applied in various medical fields.

Oncotherm GmbH
Belgische Allee 9
53842 Troisdorf
Germany

www.oncotherm.com