Combining hyperthermia with other anticancer methods

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Opening ceremony of “New-Hope” clinic
1997
You need more than 2 hands to pull a car out of the mud

You need more than one treatment method to fight cancer
HYPERTHERMIA IS AN EXCELLENT • NON-TOXIC ANTI-CANCER METHOD THAT SHOULD BE A PART OF THE TREATMENT OF ALMOST ANY CANCER PATIENT, WITH OR WITHOUT OTHER TREATMENT METHODS

Combining hyperthermia

• **With conventional methods:**
  Surgery
  Chemotherapy
  RT
  Hormones
  Biologics
  Hyperbaric oxygen
  PDT

• **With integrative oncology methods:**
  Different types of hyperthermia
  Supplements
  IVC
Hyperthermia and Surgery

Pre-operative hyperthermia
Hyperthermia may be a part of neoadjuvant preoperative treatments.
Aim is to reduce tumor size for a better surgery and prevent tumor cells spread during the operation.
The question: how many days before surgery should we stop the HT?
Case report: A 55 YO male with pancreatic cancer. HT was given 3 weeks before a Whipple surgery by a daily treatments until 3 days before surgery.
According to surgeon, surgery was very difficult due to very loose tissues.
Patient is alive and well today 6 years later.

Esophageal Cancer: Neoadjuvant Hyperthermo-Chemoradiotherapy

- Department of General Surgical Science (Surgery I), Gunma University, Graduate School of Medicine, Maebashi 371-8511, Japan.

- Results of neoadjuvant hyperthermo-chemoradiotherapy (HCRT) using weekly low-dose docetaxel followed by surgery in patients with advanced esophageal squamous cell carcinoma.
- In the 24 patients, the response rate was 41.7%.
- The 3- and 5-year survival rates were 56.3% and 50.0%, respectively.

- **CONCLUSIONS**: Esophagectomy after docetaxel HCRT may have potential for prolonging survival in patients with locally advanced esophageal cancer.
Rectal Cancer: Preoperative radiochemotherapy in combination with deep regional hyperthermia

Department of Radiation Oncology, University Hospital Tuebingen, Hoppe-Seyler-Strasse 3, Tuebingen, Germany • Int J Hyperthermia 2016;32(2):187-92

• A randomized study
• In total 103 patients with locally advanced non-metastatic rectal cancer were treated preoperatively with either neoadjuvant radiochemotherapy alone (n = 43) or the same treatment with additional deep regional hyperthermia (n = 60)
• RESULTS: Patients receiving additional hyperthermia had excellent 5 years local of 98% compared with 87% in the radiochemotherapy only group.
• Five-year rates for OS (88% versus 76%), DFS (77% versus 73%).
• CONCLUSION: Radiochemotherapy combined with hyperthermia resulted in excellent long-term local control

Combining different hyperthermia devices
Locally advanced breast cancer (refused surgery) treated with EHY-3000 to the whole chest and superficial hyperthermia

Before treatments

After treatments
Hyperthermia and Radiotherapy

Hyperthermia complements radiation:
- Preventing radio-resistance
- Hyperthermia is effective against radio resistant cells:
  - Cells in G2 phase
  - Hypoxic cells
  - Low pH tissues
- Hyperthermia prevent sub-lethal damage repair in the cancer cell through the effect on DNA repair enzymes.
- Hyperthermia increases oxygenation of tumor cells, rendering the tumor more radiosensitive

RT+Hyperthermia
Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis

- Center for Radiation Oncology KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland; Department of Radiation Oncology, University Hospital Zürich, Zürich, Switzerland

*Int J Radiat Oncol Biol Phys*, 2016 Apr 1;94(5):1073-87

- Thromoradiation therapy enhances the likelihood of CR rates in locally recurrent breast cancers (LRBCs) over RT alone by 22%

  For even those previously irradiated, reirradiation with HT provides locoregional control in two-thirds of the patients.

- Thromoradiation therapy could therefore be considered as an effective and safe palliative treatment option for LRBCs.

Local control rate after the combination of re-irradiation and hyperthermia for unresectable recurrent breast cancer: Results in 248 patients

- The Netherland group


- We evaluated the efficacy and side effects in patients treated with re-RI and HI for irresectable locoregional breast cancer recurrences.

- The CR rate was 70%. at 1, 3, and 5 years LC was 53%, 40% and 39%.
- OS was 66%, 32%, and 18%, respectively. OS after 10 years was 10%.
Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: Results of the randomized RADCHOC trial.

- The Netherlands group of radiotherapy and oncology hospitals
  Radiother Oncol, 2016 Feb 17

- Chemoradiation (RT-CT) is standard treatment for locally advanced cervical cancer (LACC).

- Patients with locally advanced cervical cancer (LACC) were randomly assigned to RT-CT or RT-HT

- Data suggest comparable outcome for RT-CT and RT-HT.

Definitive radiotherapy plus regional hyperthermia for high-risk and very high-risk prostate carcinoma

- University of Occupational and Environmental Health, Kitakyushu, Japan.
  Int J Hyperthermia, 2015;31(6):600-8

- Data from 82 patients treated with RT plus HT and 64 patients treated with RT alone were retrospectively analyzed.

- CONCLUSIONS: The addition of HT to RT may improve DFS for patients with high-risk or very high-risk prostate cancer.
HYPERTHERMIA AND CHEMOTHERAPY

- Hyperthermia increases size of blood vessels to the tumor allows more chemo to get inside the tumor.
- Blood vessels outside of the tumor are narrowed so chemo stays longer inside the tumor.
- Hyperthermia delays the appearance of MDR (Multi-Drug-Resistance).

Chemotherapy and Hyperthermia

- **Synergistic effect** with doxorubicin, Doxil (pegylated liposomal doxorubicin), cisplatin and carboplatin, epirubicin, mitoxantrone, mitomycin, BCNU, bleomycin, ifosfamid, cyclophosphamid, taxol, campto and gemzar.

- **Additive effect** with 5FU, vincristine, vinblastine and methotrexate.

- Delay MDR
Hyperthermia combined with chemotherapy for patients with residual or recurrent esophageal cancer after definitive chemoradiotherapy.

- Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan

- Salvage HCT after dCRT was performed in 11 patients with residual or recurrent oesophageal cancer.

  Complete response and stable disease was achieved in three and five patients, respectively; symptoms were improved in the remaining three patients.
  The median survival time after HCT was 12 (range=3-88) months.

Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: A systematic review with conventional and network meta-analyses

- Centre for Radiation Oncology, KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland and Department of Radiation Oncology, University Hospital Zurich

- Comparing HTCTRT, HTRT, CTRT and RT alone was conducted.

  The pairwise comparison of various groups showed that HTRTCT was the best option for both CR and patient survival.
Effectiveness of Regional Hyperthermia With Chemotherapy for High-Risk Retroperitoneal and Abdominal Soft-Tissue Sarcoma After Complete Surgical Resection


- To determine whether regional hyperthermia (RHT) in addition to chemotherapy improves local tumor control after macroscopically complete resection of abdominal or retroperitoneal high-risk sarcomas
- 149 patients were identified with macroscopic complete resection (R0, R1) of abdominal and retroperitoneal soft-tissue sarcomas (median diameter 10 cm)
- Seventy-six patients were treated with EIA (etoposide, ifosfamide, doxorubicin) + RHT versus 73 patients receiving EIA alone.
- In patients with macroscopically complete tumor resection, RHT in addition to chemotherapy resulted in significantly improved local tumor control and DFS.

Combining Mitomycin C and Regional Hyperthermia in Patients with Nonmuscle Invasive Bladder Cancer

- Departments of Radiation Oncology and Urology (TMDR, JdIR), Academic Medical Center, Amsterdam, The Netherlands. J Urol. 2015 Nov;194(5):1202-8

- 20 patients with intermediate and high risk nonmuscle invasive bladder cancer were treated with intravesical mitomycin C (40 mg) combined with regional hyperthermia.

- The 24-month recurrence-free survival rate was 78%.
• **January 2010:** 62 Y.O with adenocarcinoma of pancreas, liver and lung metastasis. No surgery.

• Chemotherapy FOLFIRI+ Hyperthermia to abdomen and lungs, HDVC and supplements.

• **August 2012:** no metastasis in the liver and lungs. Operated to remove the pancreatic tumor: no tumor cells found.

• **2013:** died of multiple bone metastasis.
August 2012

ABDOMEN

LUNGS

Hyperthermia and Hormones

- Quercetin and tamoxifen sensitize human melanoma cells to hyperthermia.
  We observed that both quercetin and tamoxifen synergize with hyperthermia (42.5 degrees C)
  G. D'Annunzio' University, Chieti, Italy.
  Melanoma Res. 2001 Oct;11(5):469-76

- Tamoxifen and chemotherapy (CTX, DTIC or Cisplatin) enhance hyperthermia effect on melanoma cells.
  Clinic of Oncology and Radiotherapy, University Hospital Center Zagreb, Zagreb, Croatia.
  Tumori. 2012 Mar-Apr;98(2):257-63
Hyperthermia and biologic therapy

- In this study we treated mice inoculated LLC tumors with hyperthermia or molecular target drugs (erlotinib 25 mg/kg/day and sorafenib 10 mg/kg/day).
- Both of hyperthermia and molecular target therapy reduced not only tumor growth but also lung metastasis.
- A combination therapy of hyperthermia and molecular target therapy reduced more of the tumor growth and lung metastasis synergistically.
- Apoptosis was enhanced by hyperthermia and molecular target drugs synergistically.


Hyperthermia in combination with gefitinib in patients with advanced NSCLC

- West China School of Medicine, Sichuan University, Chengdu, China

- Eleven patients who responded to first-line gefitinib treatment were treat with 250 mg gefitinib daily. Local radiofrequency hyperthermia was administered twice a week until tumor progression
- Median progression-free survival was 22 months and median overall survival was 26 months
- Hyperthermia improve and prolong the action of gefitinib.
Cisplatin, Hyperthermia, and Lapatinib in Patients With Recurrent Carcinoma of the Uterine Cervix

- Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands Oncologist. 2015 Mar; 20(3): 241–242.

- Eight patients with previously irradiated recurrent cervical carcinoma 6 weekly administrations of 70 mg/m² cisplatin combined with locoregional hyperthermia. Daily lapatinib was added on days 1–56.

- One CR, one PR and four SD

- The observed complete pathological response is intriguing and warrants further investigation

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Supplements enhance Hyperthermia effect

- Quercetin
- Alpha Tocoferol Acetate
- Vitamin C
- Poly- Unsaturated Fatty Acids (PUFA): EPA, DHA, GLA
- K1 and K2
- Curcumin
Quercetin and Hyperthermia

- Quercetin enhance the reversal effect of hyperthermia on MDR when combined with chemotherapy.
  Affiliated Hospital, Academy of Military Medical Sciences, Beijing, China.

- Quercetin neutralize the efficiency of Hsp70 thus it enhance the apoptotic effect of hyperthermia on cancer cells
  West China Hospital, Sichuan University, Chengdu, People’s Republic of China.

Hyperthermia and EPA

- Oral EPA specifically increases the susceptibility of liver tumor tissue to lipid peroxidation, and hence enhance the antitumor effect of hyperthermia and prolongs survival.
  Kyoto Prefectural University of Medicine
Vitamin-C and Hyperthermia

• **Enhancement of radical intensity and cytotoxic activity of ascorbate by hyperthermia.**
The combination of hyperthermia and ascorbate treatment might produce higher antitumor activity.

• **Enhanced inhibitory effects of hyperthermia combined with ascorbic acid on DNA synthesis in Ehrlich ascites tumor cells grown at a low cell density.**
Department of Radiology, Osaka City University Medical School, Japan Cancer Biochem Biophys, 1995 Jan;14(4):273-80

CURING HCC with HDC and Hyperthermia

• V.E: Hepato-Cellular Carcinoma
1993 HCC

• 1998 multiple hepatic and extra-hepatic metastasis
Failed all conventional treatments
Send home to die.

• Loco-Regional Hyperthermia + HDVC +supplements given intermittently for 2 years.
Complete Response= all tumors disappeared.
AFP 5000→ 20
Follow up for 8 years=NED.
At this stage, the patient was referred to Prof. Briner Josef in Tel-Aviv. She was treated there by non-conventional treatment by external heating. Detailed data are not available to us regarding the therapeutic approach and its beneficial effects. However, a dramatic response was achieved. AFP levels dropped to 27 (starting from ~ 1000) and CT studies showed shrinkage of the masses. Last CT studies showed no masses. Since then she is treated by Prof Briner with monthly maintenance injections of “VG1000”. We do not have any information about these therapeutic approaches but there is a dramatic response. At this stage I recommend that our patient maintain this therapeutic modality as it is revealing a good response and although I do not have enough data despite numerous attempts to retrieve this information.

Photo Dynamic Therapy (PDT) and Hyperthermia

- Synergistic effect of photodynamic therapy with hypercin in combination with hyperthermia on loss of clonogenicity of RIF-1 cells.

Combining hypercin-mediated PDT treatment with hyperthermia could significantly enhance the cell death by necrosis as indicated by morphological examination and significant loss of membrane integrity.

- Laboratorium voor Farmaceutische Biologie en Fytofarmacologic, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Leuven, Belgium

Carboplatin plus Hyperthermia and Hyperbaric Oxygen Treatment

• In animal cancer models, several studies with combined treatment of hyperbaric oxygen (HBO) and various chemotherapeutic agents have shown decrease in tumor growth.

Paclitaxel and carboplatin plus regional hyperthermia and hyperbaric oxygen

• Twenty-two patients with NSCLC with multiple pulmonary metastases received paclitaxel carboplatin and Hyperthermia (HT) of the whole thoracic region. 16 (72%) of 22 patients received hyperbaric oxygen (HBO) treatment.

• Fourteen (64%) of 22 patients had an objective response. The median time to progression of disease in all patients was 8 months and in 16 patients with HBO was 9 months.

• Department of Radiology, University of Occupational and Environmental Health, Kitakyushu, Japan

10 y/o male
2009 – Ependymoma diagnosis
s/p 7 neurosurgeries
s/p 2Xradiotherapy courses
s/p VP-shunt d/t hydrocephalus

02/2014 – started HBOT (currently 100 sessions)
02/2014-started whole-brain Hyperthermia 2-3/week

Frontal lesion

02/2014
05/2014
07/2014
CONCLUSION

• Hyperthermia is an effective anti-cancer treatment method.

• Hyperthermia is synergistic with most other anti-cancer treatment methods and should be a part of any treatment regimen.