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Cases that respond to Oncothermia monotherapy

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Cases that respond to Oncothermia monotherapy

Abstract

There is a long history of hyperthermia in oncology, but its wide range acceptance and application is missing even today. A new approach of oncological hyperthermia, oncothermia, looks promising modality of the complementary treatment of advanced malignant cases. Our present article is targeting this method, trying to answer on 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.

Background

Despite 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 therapy 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 complementary 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 non-homogeneously 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.

Hyperthermia as a treatment modality is battling for the step from the bio-medical experiment status to a clinically proven one [5], [6].

The central problem of the forced heating in a local/regional volume is the physiological feedback reaction acting to compensate the compulsory temperature elevation. The main physiological feedback mechanism is the active blood-flow in the heat-targeted volume, [7], [8], [9]. The intensified blood-flow is excellent heat-exchanger, cooling down the heated volume and effectively increasing the temperature in the sorrounding of the target. The high blood-flow delivers extra nutrients (malinly glucose) supplying the tumor, as well as increases the risk of dissemination of malignant cells by the blood-stream. Both effects are contrary to our direct aim to destroy the cancer. The situation is a competition now between the cellular distrotion by direct heat and the supply of the growth of the tumor together with its increasing dissemination ability. This is the origine of the contradictiong results and the missing satisfactory control on the oncological heat-treatments.

Technically a huge variety of heating could be applied by heat therapies [10]. Its energy-production, its selectivity, locality, kind of energy-delivery, locality invasivity control, applied frequency of the electromagnetic waves, as well as their medical applications and combination with other methods make

the heat-therapies different.

Oncothermia is a special heating, targeting the membrane of the malignant cells [11]. This nano-range heating makes possible to destroy the malignant cells by extreme temperature gradient on their membranes individually [12], without exciting of the physiological feedback mechanisms; without considerable blood-flow increase.

Our objective in this article is showing on actual cases how oncothermia works. The main addressed questions are:

- 1. Which adverse effects has oncothermia by dose-escalation (extended treatment duration)?
- 2. How the long treatment is effective in various cases of the disease?
- 3. Can we apply oncothermia as monotherapy for a long time?
- 4. Are we able to handle the fatal cancer cases as chronic disease in the style of dialysis?

Method

There were chosen numerous cases, having complications with the gold-standard therapies, in high-line treatments. Oncothermia was applied or complementary to chemo- and/or radiotherapy or it was applied as monotherapy in the cases, when the combination was not feasible. The study was started in Dec. 2011, and summarizes the results until Sep. 2012.

Patients were the intention to treat (ITT) population, no cohort was formed, a retrospective datacollection is the basis of the evaluation. The study was performed in single-institute basis and the patients were rigorously diagnosed, checked and followed-up during the trial. All together 216 patients were treated in this time with 4263 sessions cumulatively. From this we had chosen 16 cases characteristically showing the results.

We used the EHY2000+ device (Oncotherm GmbH, Germany), applying the 20 and 30 cm diameter electodes in step-up heating protocol. The maximal energy was 150 W, duration of a session was 60 min each, $2 \sim 3$ times/week, 12 times in one cycle. Average number of the treatment was 33 sessions or 4 cycles, the duration the time of the full cycles was over 6 months.

Case-reports

Rectosigmoid cancer with liver metastasis

A 43-year-old Asian man was diagnosed as Rectosigmoid Cancer with metastasis of liver in March/10/2012. and T-loop End Colostomy was performed on May/7/2012. Avastin-FOLFOX chemotherapy was given 3 times after operation and the second line FOLFIRI chemotherapy was given 3 times. He received Radiotherapy at Liver delivering 18 Gy in 10 fractions for 2 weeks from August/13/2012 to August/27/2012 and concurrent Oncothermia 37 times from July/20/2012 to Novemer/21/2012.



Before oncothermia

After 12 times of oncothermia After 31 times of OncoTx

Tumor mass in liver was regressed and liver parenchyma increased gradually with concurrent small dose of radiation and oncothermia. No adverse effect originated from oncothermia was observed. This result gives the large possibilities of combined treatment of oncothermia with low dose of radiation for far advanced cancer for palliative treatment.

Hepatocellular carcinoma

A 61-year-old Asain man was diagnosed as Hepatocellular carcinoma. TACE was given on Feb/17/2011. He suffered from Type B virus-Hepatitis from 1992, and liver cirrhosis from 2001. TACE could not be

given anymore after one time even though HCC was aggravated with elevation alphafeto-protein level in serum. Regrowing cancer and rapid rising of alphafeto-protein (20.48 to 448.90) appeared in Nov/2011. 24 times of Oncothermia were given from Nov/21/2011 to Feb/27/2012.



2 months before oncothermia

Just before oncothermia



After 24 sessions of oncothermia

7 months after oncothermia

Alphafeto-protein level was lowered and kept stable at 24.39 after oncothermia to July 2012. Tumor mass was stable until new lesion in liver found in Sept/2012 with the high elevation of alphafeto-protein to 697.40 after 7 months from oncothermia.

Pancreatic cancer

A 59-year-old Asian woman had been diagnosed as Pancreatic cancer in Aug/2010. Chemotherapy was given many times as much as possible at other hospitals.

She visited Kosin University first in Aug/2011 just only to relieve massive pain for serious carcinoma peritonei with conglomerated mass attached at anterior abdominal wall. Radiation therapy was given 30 Gy in 10 fractions(once/day, for 2 weeks) With IGRT technique to anterior abdominal wall mass in August/2011. Ascites was not at that time.

Abdominal pain was relieved much just after palliative Radiation Therapy but progressed gradually from Oct/2011.

Ascites and intestinal obstruction were developed. Intestinal bypass surgery was recommended by surgeon but was not performed. It was difficult to recover from the high risk of the operation since the patient had far advanced cancer and poor general condition.

Oncothermia was started firstly in our hospital as soon as installed in November 2011. She could eat some food and ascites was controlled by medicine since 5 times of oncothermia were given. Cancer mass was regressed a little bit. Amount of analgesics intaken was reduced.

She maintained well with oncothermia to later June 2012. But her cancer became worse gradually. Eventually cancer metastasis to both pleural cavity was developed with both pleural effusion. Patient's general condition became worse gradually for pleural metastasis. That was drained often to reduce dyspnea. It was difficult to keep hyperthermia for 1 hour due to the poor general condition and inevitably carcinoma peritonei became worse from August 2012.

She died due to pneumonitis with massive pleural effusion on the early September 2012.



Although she had a massive abdominal pain because of far advanced carcinoma peritonei, she lived for 10 months by controlling the massive abdominal pain with Oncothermia. She was the first patient to be applied Oncothermia. From her case, there are many possible cases applied to other patients of advanced cancer with oncothermia without any negative side effects.

Total 82 times of oncothermia to her were given by $2\sim3$ times/week to her for 10 months. It can be possible to apply many times of oncothermia for advanced cancer without any complications.

Synovial sarcoma

This 48 years old female was diagnosed as synovial sarcoma and received operation of right thigh in 2004. She used to live well until the recurrent and metastatic cancer was known at the right lung in September 2011.

Radiation therapy 30 Gy in 10 fractions for 2 weeks to tumor mass at right lung mass with IGRT technique was given carefully in April 2012. She lost left lung by tuberculosis when she was young. Tumor mass regressed partially after radiation therapy but progressed in November 2011. She received oncothermia 39 times from November 2011 to April 2012.



Just before OncoTx



12 times of OncoTs



36 times of OncoTx

Metastatic sarcoma to lung was markedly regressed with oncothermia. Sarcoma has been already known to be sensitive to hyperthermia. And also Sarcoma is sensitive to oncothermia as well.

Pancreatic cancer

A 49-year-old Asian man has been diagnosed as Pancreatic Cancer in Nov/2011. Chemotheray was given in Mar/2012. Brain metastasis was developed and 30 Gy Radiation Therapy in 10 fractions to the whole

brain was given in Mar/2012. Urinary Bladder metastasis was found in May/2012. Oncothermia 12 times(3 times/week) to pelvis for metastatic bladder cancer were given from May/14/2012 to June/13/2012. Oncothermia 26 times to pancreas were given from June/25/2012 to August/30/2012.



Before Oncothermia



After 12 times of oncothermia

Metastattic bladder cancer was regressed prominently after 12 times of oncothermia. Pancreatic tumor mass was also reduced in the size prominently after oncothermia. If the primary tumor was sensitive to oncothermia metastatic cancer is also sensitive to the oncothermia. But she got sudden death on Sept/3/2012 due to brain edema for aggravation of metastatic brain tumor.

Adenoid cystic carcinoma

A 56-year-old woman was diagnosed as adenoid cystic carcinoma of submandibular gland and received operation(mass resection & right maginal mandibulectomy and reconstruction with forearm Free flap, Lt. and Lt. FTSG from Lt. forearm sural nerve graft) in June/1/2009.

She used to live well up to find recurrent cancer and metastasis to lung in May 2011. She refused any treatment like chemotherapy after she heard less effectiveness and greast negative side effects of chemotherapeutic agent for adenoid cystic carcinoma. Dyspnea and blood tinged sputum developed occasionally from May 2012.

She received Radiotherapy delivering 30 Gy in 10 fractions(once/day) for 2 weeks in June 2012 and concurrent Oncothermia 48 times(2~3 times/week) from June/12/2012 to October/2/2012.



May/31/2012(before OncoTx)



July/9/2012(after OncoTx & RTx)

Tumor mass at left hilum was regressed markedly in chest CT scan after 24 times of oncothermia with 30 Gy of Radiation therapy. Adenoid cystic carcinoma is generally resistant to Radiation therapy. But concurrent Radiotherapy and Oncothermia made these metastatic lung cancer reduced in size.

Lung cancer

A 55-year-old Asian man was diagnosed as lung cancer(adenocarcinoma) in March 2010 and received chemotherapy and target therapy.

He received Radiotherapy at regrowing lesion with invasion to spine at the operated site and Rib delivering 30 Gy in 10 fractions for 2 weeks in April 2011. tumor mass regrew and multiple metastatic lesions was appeared in both lung. Oncothermia was given 24 times(2~3 times/week) from April/10/2012 to July/12/2012.



Before HTx

After HTx 12 times

Tumor mass was regressed at the right lung and spine. However tumors were progressed in the left lung because oncothermia was not given at the left lung.

Back pain to the right chest was subsided after oncothermia. Many cases were shown the reduction of the metastatic bone pain with oncothermia.

It is possible to apply oncothermia to reduce metastatic bone pain with a variety of cancer.

Bladder cancer

67-year-old Asian man was diagnosed as bladder Cancer(transitional Cell carcinoma) in April 2008, Operation and 6 cylces of chemotheray were performed in 2008.

Recurrent cancer in bladder was known in April 2011. Partial resection and chemotherapy were performed again after known recurrent cancer. But baldder cancer was progressed in spite of chemotherapy in April 2012.

Oncothermia 24 times were given from April/30/2012 to July/31/2012.



Before Oncothermia



After 24 times of oncothermia



After 12 times of oncothermia



2 months after 24 times of oncothermia

Tumor mass of bladder was regressed after 24 times of oncothermia. As can be seen the result of CT scan taken after 2 months stopped oncothermia, the futher regression of the tumor mass was observed. That is, even though the oncothemia treatments was stopped, the effectiveness in the reduction of tumor mass was kept for 2 months.

Lung cancer

This 47year old female was diagnosed as Lung Cancer(adenocarnoma) in April/2010 Chmotherapy and target therapy were given up to Oct/2011. However, no longer those treatments were affected to the patient from the early Dec. 2011.

12 times of Oncothermia (2~3 times/week) were given from Dec/22/2011 to Feb/2/2012.



Before OncoTx After 12 times of OncoTs

4 Months from OncoTx

Tumor mass was regressed markdely just after oncothermia. However tumor mass was progressed rapidly in 4 months of stopping oncothermia. Original tumor mass in the area of oncothermia was regressed. But new lesion at the outside of oncothermia region was progressed gradually.

She died in Aug/2012 due to liver, brain, multiple bone metastasis and massive aggravation of the lung cancer.

Pancreatic cancer

A 68-year-old Asian man was one of patients who received many times of oncothermia. Pancreatic cancer was diagnosed in August 2011. He refused chemotheray from diagnosis. Operation was impossible to be performed at the time of the diagnosis. Oncothermia9@~3 TIMES/WEEK) was given 65 times from February/16/2012 to October/11/2012.



Before OncoTx. After OncoTx. 12 times After OncoTx. 24 times After OncoTx. 60 times



Before OncoTx. After OncoTx. 12 times After OncoTx. 24 times After OncoTx. 60 times

He was treated 65 times of oncothermia for pancreatic cancer without any negative side effects for 8 months. In the area of Oncothermia treatment, the tumor mass was gradually reduced. However, tumor mass in the outside of Oncothermia area was significantly increased. Therefore, Oncothermia monotherapy is available to reduce pancreatic cancer.

Ovarian cancer

A 70-year-old Asian woman was diagnosed as Ovarian Cancer and RAH with both salphingooophorectomy was performed on Oct/6/2011

Cisplatin chemotherapy was given once just after operation. But she refused further treatment due to toxicity of chemotherapy. No special treatment was given from Nov/2011. Regrowing mass at left ovarian site and carcinoma peritonei was known in Jan/2012. Oncothermia was given 12 times (3 times/week) from Feb/15/2012 to Mar/19/2012.



Before oncothermia



1 month after 12 times of oncothermia

Tumor mass recurred from post ovarian cancer in pelvis was regressed markedly after oncothermia 12 times and ascites was improved and controlled by medicine.

Stomach cancer

This 50 years old man was diagnosed as stomach cancer(adenocarcinoma) and received operation(subtotal gastrectomy) in May 2009. Recurrent cancer has been found at anastomotic site of stomach and obstruction of duodenum was developed in April 2012. Stent was inserted into duodenum and antrum of stomach in April 2012. Radiation therapy delivering 30 Gy in 10 fractions(once/day) for 2week at stent site by IMRT was given between Aug/23/2012 and Sept/6/2012. Oncothermia was given 12 times by 2~3 times/week between Sept/4/2012 and Oct/20/2012 after radiation therapy. Tumor maker CEA in serum was decreased from 5.41(Aug/14/2012) to 4.44(Oct/30/2012).



Before Oncothermia



After 12 times of oncothermia

Any negative side effects were not appeared even though the high temperature had been expected at the metal stent site. Metal stent in the canal or duct is not absolute contra-indication for oncothermia. Duodenal stent disappeared after oncothermia but patient could eat food well with good food passage through duodenum. Tumor mass maybe was also regressed by oncothermia.

Stomach cancer

54-year-old woman has been diagnosed as Stomach Cancer with metastasis to right ureter in Jan/2012. The patient had inoperable state and refused chemotherpy by herself. 36 times($2\sim3$ times/week) of oncothermia were given from April/17/2012 to Sep/6/2012.



Before oncothermia

After 36 times of oncothermia

Tumor mass was regressed prominently in stomach and she could eat food from 12 times of oncothermia. The total 36 times of oncothermia were given without any negative side effects.

Rectal cancer

A 47-year-old Asian woman was diagnosed as rectal cancer and received operation in April 2010 and followed by chometherapy.

She lived well until multiple metastatic cancers were found at both lung in January 2012. She received chemotherapy and oncothermia at left lung for recurrent and metastatic cancer. Oncothermia was not able to be applied at both lung because of the limitation of RF plate. Oncothermia was given 23 times(2~3 times/week) from March/30/2012 to July/31/2012.



Chest X-ray checked at 12 times of Oncothermia revealed the regressed tumor masses at left lung prominently but ones in right lung were not reduced in size because oncothermia was not given at right

lung. CT scan was checked, too. Tumor mass regressed prominently at left lung. However those at right lung did not regressed in size, furthermore some progressed. And the pain posterior to left upper chest because of metastatic cancer with invasion to chest wall was also relieved after oncothermia. This case is not oncothermia monotherapy but It must be sure in this one film that the combined chemotherapy with oncothermia is more effective certainly.

Renal cancer

A 61-year-old man was diagnosed as renal cell carcinoma in Jan/2011. He refused to get any special treatment for cancer like chemotherapy, hormonal therapy, target therapy, operation and radiotherapy. He received only oncothermia 24 times(2 times/week) to tumor mass at left upper abdomen from Dec/2/2011 to Feb/23/2012 for 3 months.





Before oncothermia

24 times of oncothermia

Lung

A 86-year-old man checked Computerized tomography (CT) scan due to symptoms of the upper respiratory infection. CT scan showed a mass at the right lower lung and mediastinal area but we could not performed biopsy because of the high risk of procedure. The patient had inoperable state and refused chemotherapy by himself. He received Radiotherapy 30Gy in 10 fractions(once/day) for 2 weeks and concurrent oncothermia 22 times(2~3 times/week) from January/27/2012 to March/6/2012.



Before Oncothermia

After 12 times oncothermia

Tumor was regressed after 22 times of oncothermia. Combined treatment of the small amount of radiation and oncothermia revealed the prominent regression of lung mass even through histologic type were not confirmed. Tumor makers of CEA 5.99 and NSE 38.97 were abnormal level in serum.

Conclusion

These cases together with the huge amount of other treatments answers on our questions, however of course further investigations and studies are mandatory. We had not observed oncothermia related adverse effects by dose-escalation. In negligible case skin erythema appeared, handled with appropriate cream. It did not terminated any further treatments.

Oncothermia could be applied in very severe cases, where other treatments are dubious or inapplicable. In this situation oncothermia could be applied as monotherapy with success. On the other hand the complementary applications of oncothermia had no any limitations for the oncothermia side of the therapy. We observed some cases which are not eligible for oncothermia, due to the mismatch of the electrodes, the bolus is not able to cover the surface smoothly. We had no contraindicated cases in our patient spectra.

The efficacy of the treatment was depending on the number of applied sessions. The long-time applications were positive for the patients in both the curative and quality of life meanings in advanced

diseases.

We observed long-time manageability of the serious stages of the cancer, making the anyway rapid fatal disease chronic, treated it longer than the anyway expected survival and the quality of life of the patients was excepted, better than in similar cases without oncothermia.

We observed feasibility and good perspectives of this method, and strongly recommend making higher evidence clinical studies for stronger approval.

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