Oncothermia Treatment of Cancer: From the Laboratory to Clinic

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Abstract

Oncothermia is a long-time applied method (since 1989) in oncology. Its clinical results excellently show its advantages, however the details of its mechanism are under investigation even today. The method is based on a self-selective process of energy concentration and targets the membrane of the malignant cell, using the temperature gradient and the beta-dispersion of the membrane proteins. To prove the theory we show the experimental evidences in vitro experiments where we showed the definite difference between the conventional heating and the oncothermia at the same temperature. In the next step, we studied some xenograft nude-mice models, verifying the temperature-dependent and non temperature dependent factors. In addition, the synergic effect with some chemotherapies were studied, having more efficacy of the oncothermia with drugs than the conventional heating. These experiments show the definite advantages of the oncothermia compared to its classical counterpart, acting on the same temperature. We have also proved the beneficial effect of oncothermia treatment in the veterinary practice Oncothermia is applied in numerous clinics and hospitals, and we would like to show some characteristic case-reports and also the clinical benefit on the survival time elongation of liver-, pancreas-, brain-, and lung-tumor-lesions.

Keywords: Cancer; Hyperthermia; Oncothermia; Electric-field; In-vivo; In-vitro; Clinical

Introduction

Hyperthermia is an ancient medical therapy, having its renaissance from the discovery of the electromagnetic energy delivery. The electromagnetic energy absorption has several favorable physiological and cellular effects promoting direct or indirect tumor-destructions without notable toxicity. Oncological hyperthermia is an ideal combination therapy and has been shown to provide synergies with most of the traditional treatment modalities. The modern oncology (Perez et al., 2004) and radiology (DeVita et al., 2004) handbooks devote extended parts on the topic, but contrary to the huge activity, acceptance is still missing. In consequence, it is not a surprise that hyperthermia has since been debated in an increasing number of books (Streffer et al., 1978; Hornback, 1984; Gautherie et al., 1982; Anghileri and Robert, 1986; Field and Franconi, 1987; Gautherie, 1990a, 1990b, 1990c; Urano et al., 1988, 1989, 1992, 1994; Seegenschmiedt and Sauer, 1993; Matsuda, 1993; Seegenschmiedt et al., 1996a, 1996b; Kosaka et al., 2001; Baronzio and Hager, 2006; Szasz, 2008) and high-ranked clinical publications. Hyperthermia in general, is accompanied by a great deal of skepticism in the community of cancer therapeutics (mainly in radiologists and oncologists), because it has controversial results and also relatively few evidence-based studies exists.

In fact, hyperthermia is an energy transfer, modifying the natural energy flows in the tumor area. However, the changes can go in either direction: the accelerated growth and promoted dissemination vs. suppression of the tumor growth and destruction of malignant cells. Therefore, how the energy is transferred has a crucial role.
The central challenge of the many times controversial results by hyperthermia are the deep-heating which turns the challenge from medical to technical. The questions are trivially arising: How to deliver energy to the deep-seated tumors? How to select between the malignant and healthy areas? How to avoid the toxicity/burning due to the false energy-delivery? How to make reproducible control and comparable dose for medical treatments? …

Oncothermia is a further development (Szasz et al., 2001) of the traditional oncological hyperthermia method (Seegenschmiedt and Vernon, 1996), using non-ionizing, low-radio-frequency to improve the results of the conventional oncology in its complementary application (Szasz, 2006a).

**Oncothermia Preclinical Studies**

Oncothermia approach to solve the challenges of the hyperthermia in oncology:

1. Apply such mechanism, which is self-selective, (the focusing in this case would be automatic); the current goes self-selectively to the malignant cells (Szasz et al., 2001; Szasz, 2007).
2. Make such internal energy-distribution, which is not doing an average heating only, but definitively works at the places where the energy could be applied on the most optimal way. The target of oncothermia is the cellular membrane. Keeping the current in the extracellular matrix the energy heats up only this electrolyte, and a heat-flow starts from the extra- to intra-cellular regions through the membrane. This heat-flow accompanied by different ionic flows and water transport, changes the Hodgkin-Huxley equilibrium, the membrane became more transparent, and at the end destroyed (Szasz et al., 2003).

These points are realized, and called this procedure electro-hyperthermia or oncothermia (Szasz et al., 2004b; Fiorentini and Szasz, 2006). Of course many theoretical considerations (Szasz, 2006, 2007), (Szasz et al., 2006, 2008) were performed to make this idea working (Szasz and Vincze, 2006; Szasz et al., 2006). Also the modern fluctuation analysis (fractal-physiology) supports the oncothermia (Szendro et al., 2001a, 2001b).

The aim of the preclinical studies was to clarify the effect of oncothermia alone and in comparison with classical heating methods. The experimental setup made possible to keep the conditions for both heating methods identical, heating in the classical way (outside plan-parallel heaters) and in the oncothermia way (outside plan-parallel condenser electrodes) (see Figure 1). The oncothermia was performed by a specially developed laboratory device for the in vitro and in vivo experimental purposes; see Figure 2.
Oncothermia is selective by the higher conductivity and higher permittivity of the extracellular matrix of malignant tissue (Szasz et al., 2008). The highly complex dielectric constant is effective in the microscopic level as well. In coculture experiments the healthy fibroblast remain intact, while the aggressively malignant melanoma cells (A431 cell line) are destroyed; see Figure 3 (Brunner, 2007).
The constrained thermodynamic transport destabilizes the cell membrane, increases its permeability, and can induce its bobbling and distortion (Szasz et al., 2003). These high-efficacy factors favor oncothermia over its temperature-equivalent hyperthermia counterpart; see Figure 4.

**Figure 4.** Lethality comparison of onco-thermia with classic hyperthermia in vitro (native microscopic images of HL-60 leukemia cells).

The setup made fine temperature control possible, allowing the keeping of heating and cooling dynamist also identical; see Figure 5. This makes identical heat-shock protein induction by the temperature changes. The temperature-dependent equality was controlled by luciferase transient transfected HEK293 cell lines (Andocs, 2008).

**Figure 5.** The dynamism of the heating and cooling is also well controlled for comparison of the two heating methods.
Despite the equal temperature curves, oncothermia produces a higher concentration of HSPs in the outer membrane and in the extracellular matrix (see Figure 6). The higher HSP concentration, in the vicinity of the malignant cells, is one of the factors for inducing apoptosis.

**Figure 6.** HSP70 distribution in A431 epithelial cancer cell-line xenografted nude mice tumor samples treated by hyperthermia and oncothermia (immuno-fluorescence microscopic images, red: HSP70, blue: cell nuclei).

Change of adherent connections (E-cadherin and β-catenin) is also an indicator of the gain of the social signals promoting the apoptosis (Szasz et al., 2008; Bremnes et al., 2002). Remarkable change could be observed on beta-catenin dynamic development by time after the treatment on HepG2 human hepatocellular carcinoma cell-line (see Figure 7). This considerable change after 24 h of the treatment is sharply different from hyperthermia on the same temperature, and supports the other observations of the non temperature-dependent processes (Szasz et al., 2008). The sudden regrouping the beta-catenin and its enrichment at the cell-nuclei could be an indicator of apoptosis (Gijn van et al., 2001).
Figure 7. Development of β-catenin by time elapsed after the treatment in comparison with untreated and hyperthermia as well as oncothermia-treated samples. Sampling: 1 h, 3 h, 24 h after the treatment; (immuno-fluorescent microscopic images, red: β-catenin, blue: cell nuclei).

Detecting the double strains of DNA (DAPI staining) and measuring the enzymatic labeled strain-breaks of DNA (TUNEL-FICT), the necrosis is highly likely in hyperthermia (see Figure 8), while in oncothermia the apoptosis looks preferred (Figure 9).
Figure 8. DAPI staining (stains the double strands of DNA only) and TUNEL-FITC staining (enzymatic label of the strain-break of the DNA) for hyperthermia 42°C.

Figure 9. DAPI staining (stains the double strands of DNA only) and TUNEL-FITC staining (enzymatic label of the strain-break of the DNA) for oncothermia 42°C.

The in vivo experiments well support the in vitro results. The excellent focusing of oncothermia can be proved by the temperature measurement in the tumor and the surrounding healthy muscle (see Figure 10).

Figure 10. Selectivity in vivo experiments: (A) HepG2 tumor xenografted nude mice with temperature measurement probes in the tumors; (B) comparative energy-absorption (temperature) measurement.

For further experiments, a xenograft tumor-model was human colorectal carcinoma cell-line (HT-29). Cell-culture was prepared in DMEM+GlutaMax, high glucose (4.5 g/L) medium (GIBCO, Invitrogen), supplemented with 10% heat-inactivated fetal calf serum (FCS) (GIBCO, Invitrogen) and gentamycin (10 µg/mL). Cells were grown in 75 cm² cell culture flasks (BD, Falcon) incubated at 37°C with 5% CO₂ in humidified air. Cultures were harvested after 0.25% Trypsin+EDTA (GIBCO, Invitrogen) treatment of subconfluent monolayers, and were washed once in DMEM serum-free medium. Afterwards, cells were resuspended in serum-free medium to achieve the desired cell concentration.

The experimental animals were developed by the Division of Animal Experiments and Experimental Animal House of the National Research Institute for Radiobiology and Radiohygiene (Budapest, Hungary). The female nude BALB/c (nu/nu) mice were maintained in a sterile environment, sterilized food and water was provided ad libitum. The tumor was induced by subcutaneously injected at the femoral region on both sides.
with $6 \times 10^6$ cells in 0.1 ml of serum-free medium, symmetrically when the animals were 6-8 weeks old and their weights were 22-25 g. Experiments started on anesthetized animals 18 days after the tumor inoculation. For the experiment we only used the animals which developed their tumors symmetrically and approximately the same size (e.g., Figure 11). Treatments were systematically made only on the right tumor of the animals, while the left was kept for individual control. For validation of the method, seven animals were untreated and their tumors were compared.

Two kinds of treatments were performed: local classical hyperthermia and oncothermia (see Figure 12). Both of the treatments were controlled by accurately measured intratumoral temperature with fluoro-optical method.

Animals were sacrificed 24 h after the single treatment. Both the control and treated tumors were removed and cut accurately at their centerline, fixed in 4% buffer formalin, and studied in pairs. Standard histological samples were made stained with hemalaun-eosin.
The method to calculate the killing rate of the treatments is a morphological comparison based on the observed pathological differences. The living part being in intensive proliferation microscopically could be easily distinguished from the necrotic part containing the dead tumor cells. We compared the area-change of the dead part of the control and treated tumor originated from the same animal. The differences are significant (see Figure 13).

**Figure 13.** The macro-evaluation of the efficacy of oncothermia in comparison with the hyperthermia in HT29 tumor xenograft. Change of the areas of dead and vivid parts in percentage of the untreated control on the same experimental animal (data average of 3 animals each). Similar experiments were carried out with the same results for A431 human epidermoid carcinoma xenograft model and GL261 murine glioblastoma model.

Comparison of hyperthermia and oncothermia combining both methods with mitomycin-c (MMC) single-dose chemotherapy in vivo at tissue and cellular level using histological examinations is shown in Figure 14. HT29 human colorectal carcinoma cell line derived xenograft tumor model in nude mouse. Two animals for hyperthermia (42°C)+3 mg/kg MMC ip. (30 min before the treatment); and 2 animals for oncothermia (42°C)+3 mg/kg MMC ip. (30 min before the treatment).

**Figure 14.** Investigating the difference of the effects of ip. administered Mitomycine C. (A) The cell killing is relative to the control tumor on the same animal. Two-two animals were measured with double tumors on each for control. (B) Hemalaun-eosin stained microscopic images of tumor samples.

The temperature dependence was also investigated (Szasz et al., 2008). The same temperature application of the two thermal treatments was tried together with the only field application (cooled back) case (Figure 15). The advantage of oncothermia was clearly shown where the electric field has a significantly higher effect as the temperature as well as having good synergy in cell-killing process (Figure 16).
Clinical Studies

Numerous clinical studies show the efficacy of hyperthermia in oncology. Both the radiative and capacitive hyperthermia solutions have important results, but many times their control has serious problems. For example, results of a cervix clinical study in combination with radiotherapy (van der Zee et al., 2000) was a
breakthrough in 2000, however, later the results could not be repeated (Vasanthan et al., 2005) and a temperature reference point was needed (Fatehi et al., 2006).

The definite problem is always the appropriate energy targeting and its adequate control, which demonstrates the quote: “the biology is with us, the physics is against” (Nielsen et al., 2001) or “the physiology is against” (Osinsky et al., 2004).

A spectacular case is shown in Figure 17 (Renner, 2007). The 67-year-old patient had complete right ophthalmoplegia due to an inoperable squamous epithelium carcinoma in sinus sphenoidalis. Radiation was applied (54 Gy) with 6 oncothermia simultaneously. The result is complete remission. The importance of the case is its near-eye application, but without involving the eye. (Note: The treatment of the eye is strictly contraindicated!).

![Figure 17. Case example of oncothermia.](image)

Other spectacular case reports show results of esophagus carcinoma of a 54-year-old male patient (see Figure 18; Sahinbas, 2006). After multiple chemotherapies, surgery, and 50 Gy radiotherapy, the tumor was progressively grown, blocking the food passage. After 6 oncothermia (monotherapy) treatments was partial food passage, after 12 was normal—no tumor-tissue was found by biopsy.

![Figure 18. Lumen-block (01.08.01.) before the oncothermia. After 6 oncothermia treatments (29.11.2001) and after 12 oncothermia (17.01.2002) the normal food passage was reestablished.](image)

A remarkable amount of retrospective clinical data is available to indicate the oncothermia effect in humans. The present collection shows some of the retrospective clinical results. These are single-arm, open-label studies for intention-to-treat (ITT) population, dominantly for the patients in late/advanced stages, where the conventional methods were fallen. Mostly the survival rate was the studied endpoint. The inclusion criteria was the inoperable and/or in progression after chemo- and/or radio-therapy. Exclusions were only the well-known contraindications of the hyperthermia: metallic implants in the treated volume, electronic supports (like pacemaker), massive ascites, inflammatory lesions, etc.

The possible negative biases were connected to the retrospective data collection. Negative is the missing randomization. Having no prospective control arm comparison is also negative. (Comparison with large
studies and databases as well as local historical data was made.) The treatments were made on a voluntary basis for ITT population, which was negative bias as well (Figure 19).

![Graph showing first-year survival rates of various cancers with large databases](image)

**Figure 19.** Comparison of the first-year survival rates of various cancers with the large databases. Improvement of the first-year survival percentages of oncothermia (advanced patients) compared to SEER and Eurocare data-weighted average.

Positive bias was the selected very advanced patient-population. Also positive is the missing “trial psycho-attention” and the entirely regular treatment conditions (no extra care is given). The primary endpoints of the studies were always the survival rate, which was evaluated by regular descriptive biostatistics and log-rank survival test.

The treatment had a minor number of erythema (<8%). No significant subcutaneous fibrosis as well as no other toxicity was observed except for the usual toxic reactions of the complementary applied conventional treatments (radio- and/or chemo-therapies). Patients reported (subjective) decrease of adverse effect of parallel conventional therapies. Most patients reported a decrease of pain and other subjective symptoms and improvement in their general well-being.

A remarkable amount of retrospective clinical studies is available to indicate the oncothermia effect in humans. It is commonly used for such a complex and very frequent tumors like lung, liver, pancreas, brain, gastrointestinal, gynecological, etc. The retrospective data are compared to the large databases (Seer, 2000; Eurocare), having the possibility of seeing the position to the best available data in a huge average. The oncothermia challenge is its small fraction only of the overall survival. Oncothermia is applied when other treatments fall, consequently the patients with long overall survival could have not observable lifeelongation, even if oncothermia was effective. The aggressive disease with short survival is a chance to indicate the efficacy. For these reasons we compare the first-year survivals rate only (see Figure 8). In this sense, oncothermia is indicated as a feasible, effective method (Szasz et al., 2005).

The median of overall survival time is also gained in most of the localizations, despite the only advanced cases in oncothermia treatments (Table 1).

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The death-rate of patients in every three months is registered in four stages of the disease, irrespective the kind of the tumor (see Figure 20). The number of patients was 53, 232, 268, and 283 in stages 1-4, respectively and the elapsed time was calculated from the first diagnosis.

Oncothermia had suppressed the death rate of the advanced cases and created an equally controllable situation for all of the stages within one and a half years.

There are studies on such difficult localization, like brain-gliomas. In a prospective Phase I clinical trial (Wismeth et al., 2009) had shown the dose escalation and safety of oncothermia and many retrospective studies were published also about the oncothermia results of this localization. The most important publications on brain treatments were on prestigious conferences like ASCO (Hager et al., 2003; 2008), ICACT (Szasz et al., 2004a), ESHO (Sahinbas and Groenemeyer, 2002), ICHS (Hager 2004; Kleef, 2004), ICHO (Hager et al., 2004a, 2004b; Hager et al., 2008), and others (Sahinbas, 2004a, 2004b, 2005; Szasz and Sahinbas, 2004; Sahinbas et al., 2006, 2007; Fiorentini, 2006). The median survival times results are significantly higher than measured in other studies as well as the age-adjusted survival being significantly higher (Figure 21).
Figure 21. Median survival of oncothermia-treated brain glioma patients, compared to the large studies and databases (RTOG, EORTC, RT, MRC, SEER) (Szasz et al., 2004).

To see more evidence, we show the retrospective data of independent clinics, having the same oncothermia protocol (see Figure 22). The data are well correspond to each other and significantly higher than the data of the large international databases.

Figure 22. The median survival and the first-year survival in comparison with different clinics, having the same oncothermia treatment protocol.

The metastatic liver tumor is a very complicated issue due to the effective cooling of the large blood flow and the sensitivity of the organ due to the chemo-toxicity from previous treatments. Our results are also exceptionally good for that organ. The colorectal liver metastasis was the topic of four different studies (Hager et al., 1999; Ferrari et al., 2007; Fiorentini et al., 2003; Panagiotou et al., 2005). The sensitivity of the liver on the chemotherapy in advanced cases (when the other chemo-treatments were unsuccessful) is well observed on the combined treatment compared to the oncothermia monotherapy; see Figure 23 (Hager et al., 1999).
Application of chemotherapy in second line gains the response rate significantly higher than was in the first line without oncothermia; see Figure 24 (Panagiotou et al., 2005).

Both the liver and colorectal tumors were treated in two independent hospitals, having identical therapy protocols. The results are supporting the significant gain of the historical results; see Figure 25.

The pancreas carcinoma is a rapid and aggressive disease, and not too many conventional hyperthermia results can be found in this location (Hager et al., 1994). Oncothermia results presented on ASCO (Hager et al., 2002) and other conferences (Dani et al., 2003; Dani, 2004) are significantly improving the achievements.
of the conventional treatments. Results were repeated in six different clinics in two countries (see Figure 26), and so the gain definitely made on statistical evidences.

Figure 26. Comparison of six independent clinics treating with the same oncothermia protocol to the SEER and Eurocare databases.

The lung is also a complicated organ for hyperthermia because of the permanent cooling-ventilation of the breathing. Oncothermia, due to the non equilibrium approach, is an excellent treatment for that as well (Hager et al., 1999; Dani, 2003; Dani et al., 2004); see Figure 27.

**NSCLC 1y survival [%]**

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Figure 27. Kaplan-Meier survival plot for overall survival of advanced Lung patients (n = 258 pts).

**Conclusion**

Our present work shows a definite advantage of oncothermia over hyperthermia. In vitro and in vivo laboratory experiments as well as the human clinical studies prove the previous theoretical calculations. The non temperature-dependent factors increase the efficacy and enhance the applicability of the treatment. Such sensitive organs like the brain, could be successfully treated with oncothermia. As well as such blood-cooled and air-cooled ones like liver and lung, are good therapeutic targets too.
Presently, some prospective studies are in progress on brain gliomas, on advanced metastatic breast carcinoma, and on advanced pancreas carcinomas.

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