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## Research Article

# Towards the Immunogenic Hyperthermic Action: Modulated Electro-Hyperthermia

Andras Szasz\*

Professor, Chair, Department of Biotechnics, St. Istvan University, Hungary

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#### ABSTRACT

Hyperthermia treatment for solid tumors is a long-used, but poorly accepted method in clinical use. Modulated electro-hyperthermia (mEHT, trade name: oncothermia®) changes the paradigm, introduces a novel, cellularly selective and immunogenic cell-ruination. The mEHT method produces tumor-vaccination, presenting the unharmed genetic information of cancer cells to immune cells [1]. The mEHT method is approved in more than 30 countries. Its phase II/III clinical applications indicate a broad perspective.

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## Introduction

Hyperthermia in oncology faces certain challenges [2]. The poor performances of the hyperthermia acceptance in the medical community developed a general opinion, blaming the physics and the technical solutions for unsuccessful processes. Modulated electro-hyperthermia (mEHT, trade name oncothermia®) represents a new paradigm of hyperthermia treatment for solid tumors, which gives a hint on how to apply physics in this complex phenomenon [3, 4]. The 30-year history of mEHT covers multiple discoveries and many publications [5]. The mEHT technique heats malignant cells selectively. Contrary to the conventional isothermal approach, it follows the natural heterogeneity of the tumor-structure by selective energy-absorption [6]. The selection uses the electromagnetic heterogeneity of the malignant lesion [7]. Furthermore, the cancer lesion drastically modifies the collective harmony in the attacked organ, which could be repaired in the timefractal modulation of the mEHT technology [8]. The main physiology parameters of malignant cells differ from their healthy counterpart. Conductivity, due to the high metabolic rate, and the variation of the dielectric constant of the microenvironments of the cells, due to the loss of intercellular bonds are higher [9, 10]. The selective frequency dispersion, which focuses on the lipid-protein interactions, chooses the intracellular proteins as targets [11, 12]. The main medical task to treat advanced malignant diseases requests that the systemic treatment is

effective on possible micro and macrometastases all over the body. The local technique of mEHT produces immune effects, which does the required systemic task [13].

### Method

The mEHT method focuses on the bioelectromagnetic field of malignant cells. It uses sophisticated technical mechanisms to select and "gently" kill cancer cells while presenting genetic information about these cells to the immune cells. This "message" carried by various proteins is able to produce the presentation of antigens, developing the T-cells for targeting and killing cancer cells all over the body.

The technique is a capacitive impedance coupled with electromagnetic heating. However, the coupling is not plane wave as usual for capacitive methods, but strict impedance tuning to the cancerous target [14]. Interconnected conductive and dielectric effects establish the base for the impedance-selection process, realizing a cellular selection [15, 16]. The mEHT technique uses 13.56 MHz radiofrequency [17]. An amplitude modulation technique supports the focusing of the electric field on the cellular membrane with a time-fractal (1/f) pattern [18]. The similarity of the electric field and temperature actions allows the creation of the desired effects [19]. Cellular selection is performed with high preciosity, showing the excitation of the rafts of the cytoplasmic

<sup>\*</sup>Correspondence to: Andras Szasz, Professor, Chair, Department of Biotechnics, St. Istvan University, Hungary; E-mail: szasz.andras@gek.szie.hu

membrane well [20, 21]. The selective heating of the membrane rafts affects the cytoskeleton and its polymerization too [22, 23]. The physical effects of the mEHT method are described with various aspects, discussing the non-thermal energy-exchange possibility in connection with thermal conditions [24-27].

The dose in the selective heterogenic heating differs from the general dose concept of conventional hyperthermia [28, 29]. This dose is based on energy absorption, similarly, to ionizing radiation therapies [30]. Energy absorption depends on the absorbed power and of course, is connected to the temperature that produced it, but it describes the real effects more accurately [31]. It is a generalization of the conventional hyperthermia dose [32]. It is a real advantage that the penetration depth of the selective heating is larger than what the isothermal heating achieves [33]. Importantly, the heat-up period of the treatment, when the energy absorption is quasi-adiabatic, provides the best effect, offering the optimization of the treatment protocol [34].

#### Discussion

mEHT has a long history from laboratory experiments to human therapies [35]. The excitation of the membrane rafts is accompanied by the point-connected cells, which are common at the end of mitosis (cytokinetic phase) [36, 37]. The heat-map difference between the conventionally heated and mEHT treated cell-suspension showed certain deviations in up, and down-regulated genes in GeneChip measurement [38]. Importantly, the combination of mEHT with chemotherapy *in vitro* and *in vivo* as well as with radiation therapy *in vitro* and *in vivo* show the broad application variability of the method in preclinical experiments, which was also shown in clinical phase in both chemotherapies and radiation therapies (See details below) [39-44]. The thermal dose with temperature mapping is also shown *in vivo*, as well as the radiation equivalent of mEHT is estimated [45, 46].

mEHT causes massive apoptosis by exciting the death-toll receptors and transient reaction-potential channels of the membrane [47, 48]. The observed apoptotic cell-distraction is significantly more intensive with mEHT than with water-bath or other conventional capacitive coupling hyperthermia methods [49]. The large number of apoptotic bodies, together with the correct time-sequences of cell membrane exposure of Calreticulin, the release of HMGB1 protein, and membrane expression of HSP70 form a damage-associated molecular pattern. The spatiotemporal series of liberated molecules from the cytoplasm to the extracellular electrolyte (Calreticulin - "eat me signal", HMGB1-"danger signal", released HSP70- "info signal", and extracellular ATP -"find me signal") triggers immunogenic cell-death (ICD) [50]. ICD initiates the maturation of the dendritic cells (DCs) and forms a tumorspecific antigen presentation, shaping CD4+ and CD8+ T-cells in situ, real-time, without extra-corporal laboratory preparations. The prepared T-cells act throughout the whole body by blood flow transports, causing an abscopal effect on distant micro and macrometastases, increasing the survival time as well [51]. The concomitant application of the (anyway ineffective) unmatured DCs form antigen presentation cells (APCs), and significantly increase the survival [52, 53]. Importantly the re-challenge of the same tumor into the cured animal was unsuccessful; the process has worked like a tumor-vaccination [1].

The mEHT method has a broad application possibility in oncologic clinical use [54]. mEHT is a complementary method and could be applied together with all other conventional treatments, including chemotherapies and radiotherapies [3, 55, 56]. Importantly, the strong selective energy absorption on the membrane rafts helps the cellular killing as well as the drug penetration into the cell, and the moderate isothermal heat effect pumps the blood to the selected tumor helping the drug delivery and also improving the oxygenation which sensitizes the radiotherapy action. Oxygen delivery is strongly supported by the separation of the grouped erythrocytes (destroys the rouleaux formation of them), so oxygen delivery does not need high local isothermal temperature [57]. The moderate isothermal gain of temperature does not improve the metastatic dissemination, which could be a problem in higher heating.

Such a sensitive organ as the brain could be safely treated by a doseescalation safety trial for advanced, relapsed glioblastoma patients, and an effective curative potential was presented in this group of patients, integrated the therapy in complex manner in the clinical practice [58-60]. A larger group of brain gliomas shows the same positive effect, and another trial has detected the immunogenic behaviour in a complex integrative therapy [61, 62]. This brain treatment can be personalized, and it shows its advantages in both clinical and economic considerations in meta-analyses [63, 64]. The results in rectal cancer, gastric cancer, and others, show the gastrointestinal capability of mEHT, strongly supported by clinical trials on primary and metastatic origin of liver cancer [65-70]. The anyway problematic inoperable pancreatic cancer also shows the feasibility of mEHT in this disease [71, 72]. The worldwide problematic large morbidity of lung cancers needs the complex solutions of the therapy, which could be given by mEHT [73]. The high complexity of the therapy could use different methods complementary to chemotherapy, including mEHT too [74]. Complementary mEHT could be used together with chemotherapy and radiotherapy too, even in the aggressive small-cell lung carcinoma [75-77]. There was an interesting observation, a successful clinical study with intravenous high-dose vitamin C for heavily pretreated, advanced, refractory non-small-cell lung cancer [78].

mEHT proved its feasibility in gynaecological cancers too. Both the local tumor suppression and longer survival time were observed in advanced cervical cancers by mEHT with chemotherapy compared to chemotherapy alone [79]. Chemo-radiotherapy for recurrent cervical cancer was also more effective in case of the complementary application of mEHT [80]. A phase III extended clinical trial on local disease control in HIV-positive and negative cervical cancer shows significant improvement [44]. The survival of cervical cancer patients with or without associated HIV infection and treated with mEHT combined with chemo-radiotherapy shows the strong capability of the method for longterm measures as well [81]. An important addition is that the treatmentrelated toxicity of the mEHT was suppressed, and at the same time, the treatment improves the quality of life of HIV-positive cervical cancer patients [82]. The detailed analysis of nodal disease on PET/CT scans in patients with HIV-positive and negative locally advanced cervical cancer shows the improvement of the patient status metabolically too [83]. The treatment of ovarian cancer has also shown advantages with the complementary application of mEHT in a clinical trial, and the successful mEHT complementary treatment of advanced ovarian cancer

with thermo-chemotherapy and adjuvant immune therapy presented a significant improvement [84, 85]. Others independently showed the feasibility of complex multimodal immunotherapy for patients with ovarian cancer [86]. The complex approach showed its capability well in breast cancer too, which was also well-supported by immunotherapy [87, 88]. The larger group of breast cancer patients also proved the efficacy of the mEHT method in a single-centre experience [89]. The treatment of advanced triple-negative breast cancers by mEHT is also feasible [90].

The primary leiomyosarcoma of the breast following salvage mEHT and pazopanib, as well as recurrent metastatic sarcoma, indicates the applicability of the method in this type of solid tumors, which was proven in more cases, and in clinical trial too [91-93]. The advantages of the complex approach are shown by an 8-year observational study for the survival time of various advanced solid tumors treated complementarily by mEHT, as well as for various malignant diseases when mEHT was applied independently [94, 95]. Cases that respond to the mEHT monotherapy are also collected, showing success, and sometimes turning the acute, fatal cancer to a chronic, long-term, manageable disease [96].

The abscopal effect using the local mEHT allows the overall action in the system; it treats the micro and macrometastases in distant locations [97]. The abscopal immune actions are shown in some clinical applications for advanced metastatic cancers including brain tumors too [62, 87, 88, 98]. The potentiation of the abscopal outcome was one of the successful parameters in advanced cervical cancer treatment with mEHT and was proven in some cases in combination with radiotherapy too [99, 100]. It shows the effects of tumor-directed immunotherapy [101].

### Conclusion

The method mEHT has a broad application possibility in combination with other conventional cancer treatments or even in monotherapy application when the condition of the patient does not allow the complementary therapy. mEHT extends the local hyperthermia treatment to a systemic one by the abscopal effect, making the treatment of advanced cancers with distant metastases available.

The preclinical and clinical results support the preliminary expectations formulated on theoretical and model basis. The observed clinical results allow the development of a guideline for local hyperthermia treatment concentrating on mEHT in oncology, with the authorship of 28 physicians from 12 countries (Austria, Canada, China, Germany, Greece, Hungary, Italy, Switzerland, South-Korea, South-Africa, Spain, and Taiwan) [102].

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