Hyperthermia today: Electric energy, a new opportunity in cancer treatment

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> Abstract

Hyperthermia is an ancient, but nowadays rapidly developing treatment method in tumor-therapy. Its new paradigm applied in the electro-hyperthermia (oncothermia), which provides energy by means of electric-field and produces non-equilibrium thermal situation in the tissue. The temperature gradients formed in stationer conditions, destroy the membrane of the malignant cells and selectively eliminate the cancer tissue. The characteristic control parameter is the absorbed energy-dose, which is partly used to make the distortions, partly to increase the temperature of the target. This type of technique could be applied for some tumor sites, including brain, soft tissues, liver and abdominal masses, pancreatic cancer, head and neck tumors as well.

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Introduction

Cancer and its treatment have been one of the greatest challenges in the medical science for centuries. Nowadays, enormous economic and human resources are involved in this field, but according to the epidemic data the solution will still be awaited for. Sure, cancer is not the first and probably not the last one among the diseases which despite of the exceptional human efforts have not had any cure for a long time. The use of hyperthermia for cancer therapy has been documented for thousands of years. The first provable application was attributed to Hypocrites, whose approach of course was mainly supported by the Greek philosophy, where the fire (heat) had the highest level of abilities and freedom. The method was later forgotten. It was revived around the end of the 19th century, when the deep penetrating energy transfer was solved by electromagnetic way. As early as in 1912, a controlled Phase II clinical study on 100 patients was published, showing the benefit of the thermo-radiation therapy.[1] Nevertheless, hyperthermia is still in its starting phase, it carries all the problems of the method in early stages: not enough scientific proofs have been collected yet. The situation today is similar to that of radiology at its early stages. When ionizing radiation was first discovered, many

hypothesized its usefulness in oncology, yet its exact techniques, dose, contraindications, limits and the conditions of optimal treatment were determined only several decades later. This is a natural process: every beginning shows these development.

Hyperthermia suffers from a lack of standards and a lack of scientific consensus about its effects on malignant and healthy tissues. In order that hyperthermia will gain widespread approval and clinical use, the technique requires extensive further research and standardization. Many believe in oncological thermo-therapy and many regard it as quackery. There is a definite group of physicians who submit that hyperthermia has a strong curative force in oncology; however, another group exists believing the opposite. Sure, both the positive and the negative believers are not helpful to clarify the situation. Fortunately, science is not the question of belief; it is a question of proofs and results, which has to be carefully analyzed. We need interdisciplinary scientific approaches and hypotheses to go ahead with the topic.

There are intensive discussions in scientific communities on the mechanism of oncological hyperthermia[2] and so it's not a surprise, that nowadays most oncological conferences deal with hyperthermia. There is an increasing number of the relevant published books and periodicals as well as a large number of scientific articles published in high ranked, good impact factor journals.[3] The increasing number of applications and clinical trials at universities, clinics, hospitals and institutes prove the feasibility and applicability of clinical hyperthermia in cancer therapies.

> State-of-art

Some widely accepted effects characterize the classical hyperthermia:

• Higher baseline temperature.[4]

• Vascular changes,[5],[6],[7] increased heat conduction,[8] selective increase in tumor temperature[9] providing an effective heat trap.[10]

• Cellular membrane changes,[11],[12],[13] it can change lipid-protein interactions[14] and it can denature proteins.[15]

• Changes the active membrane transport,[16] the membrane capacity,[17] the membrane potential,[18] the cellular function[19],[20] and causes thermal block of electrically excitable cells.[18],[21]

• Increases the biochemical reaction rates[22] resulting in hypoxia[23] and anaerobe metabolism producing lactate.[24]

• Causes ATP depletion.[24]

• DNA replication is slowing down.[25],[26]

• Enhances the immune reactions,[25] with increase of natural killer cell activity[27] and distributes tumor-specific antigens on the surface of various tumor cells[28] and assists in their secretion into the extracellular electrolyte.[29]

• Hyperthermia and especially its electric field induced realization, has significant pain-reduction during treatments.[30]

• It has synergy with ionizing-radiation[31] and by chemotherapies.[32],[33]

• Could make previously dangerous operations possible.[34] Postoperative application prevents relapses and metastatic processes.[35] Intraoperative radiofrequency ablation has also been used to improve surgical outcomes.[36]

• Combination of the hyperthermia with the gene-therapy looks very promising, therapy in advanced breast cancer patients[37] and enhances the local rate of release from liposomes.[38]

Although hyperthermia can have significant benefits, there are several well-known problems to be solved.

Standardization

Hyperthermia dosing and treatment standardization is still a significant problem. Everybody agrees that hyperthermia is an overheating of the targeted tissue, but the definitions strictly differ on the heat-dose and the temperature issue.

Hot spots

Inadequate focusing can dangerously overheat the healthy tissue, causing unwanted burn and necrosis.

Heat Shock Protein (HSP) production

Heat can induce HSP production. HSP-assisted adaptation mechanisms decrease the efficacy of hyperthermia and can aid in the development of resistance to heat, chemo and radiation therapies.

Many believe that the single most important factor in hyperthermia is tumor temperature. On the other hand, there are no doubts about the strong heat-dose (energy absorption) dependence, which is shown by the treatment-time relevance in laboratory and clinical results.[39] However, the application of lower temperatures for longer time periods (same dose) treatments also showed surprisingly good efficacy for whole-body hyperthermia treatments.[40] This finding supports the opinion that the delivered heat dose (absorbed energy) or applied field[41] (electromagnetic influence) are the primary determinants of efficacy. More recently, numerous scientific theories concentrate on the vital significance of the thermally induced but basically non-thermal effects.[42] They back up their view by the thermally and non-thermally generated chaperone proteins, which are most of the case heat-shock proteins (HSP).[43]

> New paradigm: Electro-hyperthermia

Recently, scientists have begun to realize that hyperthermia induced temperature gradients could have significant biological effects. A new branch of hyperthermia, known as extracellular hyperthermia[44] (or electro-hyperthermia, oncothermia) has been developed around this concept. Although this new technique recognizes the benefits of increased tissue temperature and its biological consequences it also argues that non-equilibrium thermal effects are partially responsible for the observed clinical deviations from the purely temperature-based treatment theory.

Oncothermia is devoted to enhance the efficiency of conventional hyperthermia by additional, non-equilibrium thermal effects with the aim of suppressing the existing disadvantages of the classical thermal treatments. The electric field energy matching (capacitive coupling) has smaller penetration depth relative to the magnetic field, however, the absorbed energy is significantly increased. On the other hand, the penetration depth of the radiative (antenna-array coupled) applications is only one third of that of the capacitive coupling. Moreover the electric field offers important selectivity factors to use. The energy absorption at the applied frequency is proportional to the tissue conductivity and the square root of the dielectric constant of the targeted material. Due to its intensive metabolic activity, the conductivity in malignant tissue is higher than that of normal tissue;[45],[46] as well as the dielectric constant of the extracellular matrix at the applied frequencies is also higher in the malignant tissue than in the healthy one.[45],[47] It has also been observed that the dielectric constants in the malignant tissue are far from homogeneous[48],[49],[50] and this is supported by theoretical considerations.[51] In consequence good selectivity could be achieved at relatively low frequencies. Further focusing

effect can be derived from the coherent electric waves,[52],[53],[54] with spontaneous breakdown of the polarization symmetries. Therefore the electric coupling could select between the healthy and tumor-tissues.

The energy absorption for these effects is more significant than the temperature; so we have to characterize the hyperthermia by thermal dose and not by temperature. Thermal dose changes many energetic processes in the tissue and in their physiology. Most of the desired changes (structural and chemical) need energy consumption, which will be missing to rise the temperature. The heat, causing only the temperature rise, is not involved in the actual distortion, that is "lost" to make the job. The non-equilibrium thermodynamics describes how the absorbed heat could excite various (e.g. diffusional, electric, chemical, etc.) processes; which drives the distortion efficacy as well. These phenomena are completely out of the possibility of temperature characterization.

Electro-hyperthermia is based on a capacitively-coupled energy transfer applied at a frequency that is primarily absorbed in the extracellular matrix due to its inability to penetrate the cell membrane.[55] Although these temperature gradients typically relax within a few milliseconds, a constant energy delivery can maintain this gradient for extended periods of time. An externally applied electric field can maintain temperature gradients of 1 K/mm, creating a permanent heat flow of 1500 nW/mm 2, which is well above the natural heat-flow (20 nW/mm 2) across the target cell membranes. This gradient and the resulting heat flow can produce 150 pA/mm 2 currents through the membrane primarily by Na+ influx into the cell, which significantly exceed the typical 12 pA/mm 2 sodium efflux present. This depolarizes and therefore destabilizes the membrane and stimulates Na+/K+ pump activity. This requires ATP resulting in further heat production at the membrane. The membrane permeability of water is much higher than for ions, therefore it is the main transported component in thermo-dynamic coupling. A thermal flux of 0.001 K/nm can therefore build up pressure reaching 1.32 MPa. Since malignant cells typically have relatively rigid membranes due to increased phospholipids concentrations,[56] an increase in pressure will selectively destroy malignant cells before it affects healthy ones.

A relevant characterization of oncological hyperthermia for quality guidelines has to be started to define the aims: to destroy the malignant cells. This demand contains some more precise requests: act selectively on the malignant cells, block the further proliferation and stop the dissemination of tumor-cells, etc. The demands actually do not contain any temperature request; the temperature could be a tool only for this job. If a bio-system undergoes chemical reactions, the non-temperature terms of the internal energy become important.[57] In despite of the same temperature was reached by conventional and microwave heating, the in-vivo reaction was significantly different.[58]

In despite of its inadequate character, the temperature has gradually become the base of hyperthermia quality assurance and treatment control. The physiologically and physically well studied extracellular ionic environment is used to control the treatment, serves for comparison and gives information for the physician about the treatment success in-situ. The ion-concentration in extracellular electrolyte (ECM) definitely depends on the metabolic rate, on the chemical reactions and on the structural changes. To control the energy induced distortion processes the ion-density and the actual structural changes could be well followed by the simple technique of complex bio-impedance;[59],[60] uses special frequency dispersion of the actual tissue. As early as 1940 both the whole-body electrolyte status[61] and the local changes (ECG)[62] were studied by the method. Nowadays, it is commercially applied, (T-Scan TS2000) and for breast tumor diagnostics received the FDA approval in 1999. Various important parameters

had been measured by this method (histological,[63] coagulative necrosis,[64] apoptosis,[65] ischemia.[66],[67] In addition, the temperature of the tissue[68] and the Arrhenius activation energy[69] could be monitored by impedance. It adequately measures the distortion made by irradiation,[70] as well as the drug-effect can also be controlled,[71] moreover, the wound healing is also objectively traceable.[72] It is widely applied for RF ablation/interstitial techniques, without any extra control of the temperature.[73],[74]

> Results

OncoThermia results were mainly measured by the survival analysis (Kaplan-Meier distribution) and considered the quality of life by objective and subjective parameters. The results are amazingly good. Some examples are collected below, which are rarely treated by hyperthermia.

Brain

The brain treatment is generally out of scopes of hyperthermia with conventional methods. However, oncothermia is able to treat brain with excellent results.[75] Oncothermia is applied for the advanced brain tumors (anaplastic astrocytoma and glioblastoma multiforme)[76],[77],[78] and the survival analysis shows a great success,.(overall survival median/mean: 27.3/40.6 (n=29) and 14.1/17.4 (n=33) months for astrocytoma and glioblastoma respectively).

Liver

The liver hyperthermia is a complicated issue because of the large blood perfusion and sensitivity due to the chemo-toxicity from previous treatments. Oncothermia results are also exceptionally good for that organ.[79] Overall median survival for patients with liver metastases from colorectal primary (n=80) is also remarkable (median is 24.1 months) by oncothermia treatment.[80]

Pancreas

The pancreas carcinoma is a rapid and aggressive disease, also not much conventional hyperthermia results could find in this location. However, oncothermia has good results in survival.[81],[82],[83] The advanced pancreas carcinoma study[84] (N=129) shows also very good response for the oncothermia treatment (median/mean 8/12.5 (n=85) and 6.5/8.6 (n=34) months for active and control groups respectively).

Lung

The lung is also a complicated issue for hyperthermia because of the permanent cooling-ventilation of the breathing. Our method, the electro-hyperthermia due to the non-equilibrium approach is an excellent treatment for that as well.[85],[86] For example, oncothermia successfully applied for advanced non-small-cell lung cancer[87] (median of overall survivals (n=200) are 36.3, 20.3 and 11.4 months for not advanced, advanced (operable) and advanced (not operable) cases, respectively).

Bone

The bone is the other problematic issue for hyperthermia because of the low density of the bone compared to the adjoining tissues. Excellent bone results could be achieved by oncothermia as a part of a complex therapy.[88]

> Conclusion

Hyperthermia is an emerging effective treatment method in oncology. It has became a new modality of cancer treatments, showing significant improvements in tumor response rates and patient morbidity in combination with other treatment methods, such as surgery, chemotherapy, radiation therapy and gene-therapy or applied as a single therapy. Nevertheless, hyperthermia is still in its infancy. It lacks standards and a scientific consensus about its effects on malignant and healthy tissues and

the current techniques used to treat patients vary significantly from antenna-array focused electromagnetic energy delivery methods to non-thermal low-power current applications. In order to gain wide-spread approval and clinical use for hyperthermia, the technique requires further extensive research and standardization. Hyperthermia's update technique, the oncothermia is highly selective and safe, providing all the positive effects of the conventional hyperthermia with additional new advantages. Its working principle is mainly based on the extracellular and highly focused actions, extending the thermal treatment efficiency by non-thermal effects and by non-equilibrium selection and distortion of cellular membranes in tumors. We are convinced that the perspectives of hyperthermia in oncology are very bright and promising. What we have in hand is a practically non toxic effect with huge potential and advantages.

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