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Oncothermia as personalized treatment option

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Abstract

Oncothermia is a nanoheating technology personalized for individual status depending on the state, stage, grade, and other personal factors. The guiding line of the treatment keeps the homeostatic control as much effective as possible. One of the crucial points is the surface heat-regulation, which has to be carefully done by the electrode systems. The applied step-up heating supports the physiological selection. Recognizing the hysteresis type of SAR-temperature development the protocol could be well conducted. Using the Weibull distribution function of the transport processes as well as considering the typical physiological relaxation time of the tissues special protocols can be developed. It has wide-range applicability for every solid tumor, irrespective of its primary or metastatic form. It could be applied complementary to all the known oncotherapy methods. It is applicable in higher lines of the therapy protocols, even in the refractory and relapsed cases as well.

Keywords: oncology, hyperthermia, oncothermia, personalization, Weibull-distribution, logistic-curve, response-time, surface-cooling

Introduction

The personalization of the oncological treatments is the new trend in modern medicine [1]. Oncothermia is a personalized treatment using energy delivery to the targeted tumor [2]. This energy is well focused on cellular level [3], and makes the dose of energy optimal for cell destruction [4]. The personal feedback of the patient together with the natural homeostatic control of the treatment actions makes the treatment realistically personalized [5]. The central task is to find the proper dose in the given application, and optimize the safety and curative limits of the applied dose. The lower limit is of course determined by the minimal effect by heating and the upper limit determined mainly by the safety issues, like it is usual for overdoses. The lower limit of oncothermia dose is indefinite, because in case of normothermia nothing else has action only the complementary treatment alone, which has no danger and has such curative effect as we expect from the gold-standards. For the upper limit however there are very definite technical and physiological parameters: the surface power-density of the signal is limited by the blistering to the 0.5 W/cm^2, (60 min basis) the internal hot-spots could hurt the healthy tissue, and in systemic application the physiology anyway limits at 42°C. The ultimate challenge is the developing heat resistance, which could make the hyperthermia ineffective, the disease became refractory of heating. The presently applied dose concept (CEM) in conventional hyperthermia is physically incorrect (temperature is not a dose) and due to its inhomogeneity concept it is hard to measure. The systemic (whole body) heating in extreme case reaches the 42°C (even the 43°C is applied sometimes in special conditions; CEM100%) but the expected distortion of the tumor does not happen. The high energy of the local heating (in most of the cases more than 1 kW is applied) at the start makes vasodilatation, which turns to vasocontraction over a definite physiological threshold at about 40°C. In consequence, over this threshold the high temperature blocks the complementary drug delivery and causes severe hypoxia, which is a severe suppress of the effect of complementary radiotherapy. Furthermore, the conductivity and permittivity of the skin is physiologically controlled by the blood-perfusion, which definitely modifies all the electromagnetic applications through it.

Hyperthermia overheats the actual target. It does not limit the target size at large (like whole-body hyperthermia) or at small (like heating with nano-particles) volumes. These methods are all characterized by the temperature, but they are characteristically different by their thermal state. In whole-body heating the thermal equilibrium drives the process, the body-temperature characterizes the treatment technically. However the body temperature characterizes the process less and less by decreasing the volume of the heated target, the body temperature becomes stable and almost independent from the local heating of a smaller volume in the body. Contrary to the thermal equilibrium in whole body heating, the nonequilibrium dominates in local treatments, and consequently thermal gradients will appear in the system.

Heating in nanoscopic range creates huge fluctuations of the local temperatures while the hot nanoparticles try to equalize their high temperature with their neighborhood. This process is typical for the commercial microwave heating, where not the extra nanoparticles, but especially the water-molecules are heated in their nanoscopic sizes, and those give the temperature to the entire volume by time. To

construct a nano-heating process the targeting of the nanostructures is a clue. Their selection from the other materials makes their controlled heating and also targeting the heat on the desired volume possible.
Extra nanoparticles could selectively absorb the electromagnetic energy heating up these small particles extremely in their neighboring spheres. Our approach is definitely similar, but by not using extra particles for selective energy absorptions. Our nanoscopic targets are naturally in the body, in the membrane of the malignant cells. The selection is based on the metabolic differences (Warburg effect), the dielectric differences (Szent-Gyorgyi effect) and beta-dispersion (Schwan effect) as well as uses the structural (pathological) differences (fractal effect) of the malignant lesions.
The main medical advantages of the method are its personalized targeting together with the effective selection and distortion of the malignant cells. The new direction of application focuses on the blocking of their dissemination as well as promoting the bystander (abscopal) effect acting on far distant metastases by a local treatment. The method is successfully developed in the direction of the immune-support, and a new patent covers an exciting area: cancer-vaccination with oncothermia.

Method

The physiological processes are determined by a dynamic equilibrium process-character, which is dominantly determined by special transports and logistics in the complex bio-systems. The distribution which is typical for general logistics, failure analyses and even for survivals is the Weibull distribution [6], which cumulatively looks

$$f(x) = e^{-(x/t_0)^a} \qquad (1)$$

where to is the unit time, when the value of the function is 1/e<0.63; the a-exponent in the distribution defines the shape (see Figure. 1.).

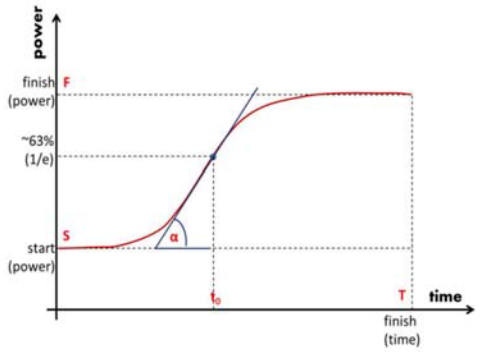

Figure 1. A special point of the Weibull function: the value, where t=t0 (1/e≈0.63). The derivative in the inflexion point equal (n/to)∙ (1/e)≈0.63*n, when to=1. The popular meaning of the parameters are: to is the stretching in x-direction (time-transformation), n is the stretching in y (incline of the curve). The parameters which has to be defined are the F, S, T, t0 and α, the finishing and starting power, the full treatment duration, the 63% of the power-increase and the slope of the power increase, respectively

The a-exponents were observed in various processes in wide range of applications. The generalized logistic function (sigmoid) could be constructed by various ways, but the so called Avrami-exponents (a, which is the exponent of the above Weibull function) are functionally appearing based on the extended works of FW. Cope [7], [8], there are some collected Avrami-exponents for various solid-state and biological processes show the universality of this logistic function.
The application of the Weibull distribution function approach multiple clinical applications and it is well established theoretically and practically, [9], [10], [11], [12]. It is used for a long time for survival description in gerontology [13], [14] and in oncology [15] as well.
The function has its inflexion point (where the tendency of decreasing changes) in t=t0 at 1/e (00.63) value. The derivative in this point is proportional to n. (The derivative there is exactly n/e [0-0.63n].) Therefore the parametric evaluation could be well checked in the t=t0 point. Note, the Weibull distribution could be well approached by normal (Gaussian) distribution over a>2. The area under the curve (shaded in the next figure) represents the complete energy-dose which is provided to the patient.

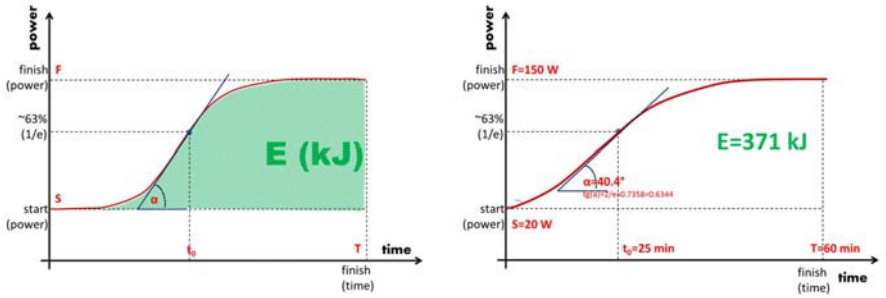

Figure 2. The provided energy is represented by the area under the curve (integral of the forwarded power, (a)), and the slope at the infexion point is proportional with the exponent "a", shown in numerical example (b)

However the continuous increase of the temperature does not fit to the homeostatic steady-state requests. Physiological response time (when the homeostatic equilibrium is reestablished after a definite disturbance) is 5-7 min. We propose at least 6 min on the definite chosen power level before the next increase step-up. Considering this transient as 6 min, the step-up heating is shown below. In this case the obtained dose is higher due to the upfitting rule, which we applied. In case of using 10 min relaxation time the protocol is shown on Figure 3.

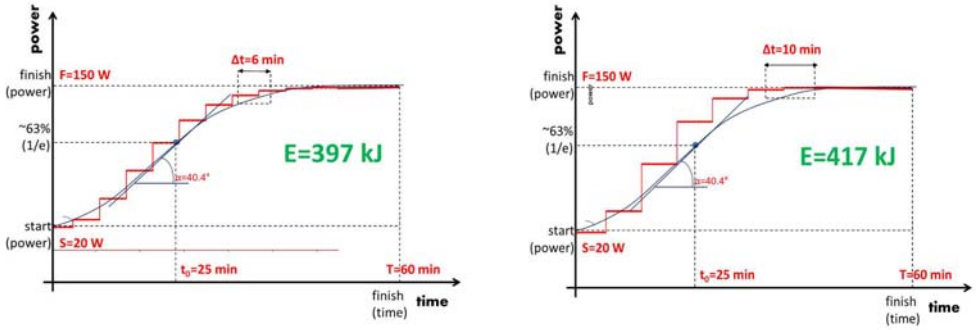

Figure 3. The step up heating follows the Weibull curve and keeps the steps until the homeostatic equilibrium. The provided cumulative energy could vary by the time-intervals of the steps

Difference between the poison and medicine is only the dose. In numerous cases people committed suicide taking medicine which would be useful in lower dosage in treatments. The dose is an important factor of efficacy safety and reproducibility too. In case of medication or radiation oncology we know the dose units as quantitative measurable values in mg/m2 or J/kg in chemo- or radiotherapies, respectively.
In hyperthermia the temperature is overemphasized as a dose, however it is not a quantitative parameter, it is a quality which makes the equilibrium spread all over the system. The temperature is an intensive parameter characteristic average of the individual energies of the small units in the system. In chemotherapy the cytotoxic remedies could cease very serious side effects, their safety has emphasized role in their applications. The chemo-doses are determined by the safety (toxicity) limits, independently of the person or the size of the tumorous target. The result (efficacy) is measured a definite time later, when the result is measurable or the toxicity (by personal variability) appears. Then the chemo-dose could be modified or complete change of the medication occurs. The actual dose varies in this second line, considering more the actual person and the actual situation.
When the medication definitely has no side effects (or the side effects are controlled) then the dose role has no upper limit by their safety, and also when the dose is limited but it is too high for the actual patient due to the biovariable poisoning limit, then the actually applied dose is of course lower, trying to fit it for the actual patient.
Oncothermia is governed by the very personalized way: the patient immediately (during the treatment and not a considerable time afterwards) sensing and note the toxicity limit: the heat-pain immediately limits the oncothermia dose. When the preset dose is too much actually it has to be modified by the personal requests. On the other hand, when the preset energy-dose is too small (the patients actually can tolerate more, the personalized toxicity limit is higher), then higher energy has to be applied until the personalized limit is indicated by the patient. Overheating is impossible, because the surface of the skin has the highest thermal load, and the heat-sensing is also there. This personalized dose regulation is the main factor of the safety and together with this for the efficacy too.

Results

Oncothermia has formulated a new paradigm [16], and made a pioneering job: it was the modulated electric field application, which later had good continuation in the literature in many laboratories worldwide. Its definite breaking results were on the modulated field effect combined with the thermal actions [17], showing large development in the present clinical practice. The electric field action was considered in serious manner in 2000 by Nature [18], and has been intensively applied in the clinical practice [19], [20]. The modulated electric field actions were applied for various accepted clinical trials [21], [20].

The second new approach was the controlled micro-heating, [22], which makes it possible to introduce the dose as the absorbed power [23], [24]; like it is used in the standard radio-therapy as well.

The third new important field which was pioneered by oncothermia is the immune-stimulative applications of the modulated electric field, showing the definite natural apoptotic cell-killing [25], [26] with activation of various leucocytes [27] to isolate [28] and kill the malignant lesion. The fourth pioneering field is the [29] abscopal (bystander) effect of modulated electric field. According to the remark of world-famous tumor vaccination researchers in their last conference, it could be a good basis to be involved in this very modern and promising field. This effect makes a great opportunity to make the local treatment systemic [30], like the locally observed tumor becomes systemic by its malignant progress.

In clinical point of view Oncothermia makes also important and unique steps to go forward with proving its trustful performance [31]. It has various levels of clinical evidences, has multiple studies including phases of the data development from the toxicity measure (Phase I), [32],[33], through the efficacy (Phase II) [34], and the wide range clinical applications (Phase III/IV) [35]. Oncothermia has many retrospective studies but also many prospective ones in Phase II and Phase III categories. The retrospective data are compared to the large databases, and compared to the multiple clinical institutions, making statistical evidences of the validity of the data.

Presently altogether oncothermia has 54 clinical trials for malignant diseases involving 2796 patients from six countries (Germany, Hungary, Italy, S.Korea, China, Austria). These trials cover 15 localization (see Table 1.) The patients were in advanced stages, mostly over the 3rd line treatment. The comparison with the large databases was made in multiple clinics relations, showing extremely large (minimum 20%) enhancement of the 1st year survival percentages.

Study	Number of studies	Number of patients (n)	1st year survival (%)	Median overall survival (m)
Brain studies	10	521	73.99	22.19
Pancreasa studies	6	184	47.04	11.02
Lung studies	5	636	64.76	15.79
Bone	3	79		40.10
Liver metastasis	7	267	86.00	18.06
Colorectal	7	447		
Gynecology (pelvic)	5	100	93.22	33.25
Breast	1	103	97.10	52.10
Esophagus	2	19	41.70	55.64
Somach study	1	68	58.90	14.40
Kidney cancer	1	39	84.60	35.90
Urinary bladder cancer	1	18	85.00	36.50
Head and neck	1	64	92.20	26.10
Soft tissue sarcoma	1	16	100.00	35.90
Prostate	3	135	88.90	38.80
SUM	**54**	**2796**		

Table 1. List of oncothermia studies. Some references of various localizations: Bone (metastatic) [36], [37]; Breast [38]; Colorectal [39], [40], [41], [42], [43]; Gliomas [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], Esophagus [54]; Brain (metastatic) [55], Kidney [56]; Liver (primary) [57], Liver (metastatic) [58], [59]; Lung (NSCLC) [60], [61]; Lung (SCLC), [62], [59], Pancreas [63], [64], [65], [66].

Conclusion

Oncothermia has good clinical achievements in the clinical studies, making a stable basis of the clinical applications in various advanced primary and metastatic malignancies and giving the long time expected stable standard on oncological hyperthermia. Oncothermia with its surface stabilized sensing (patented action) uses the personal sensing in objectivity of the actual energy-dose. This makes the accurate and personalized treatment possible by this method.

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