Electro-hyperthermia in Oncology

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Summary

Hyperthermia is a rapidly developing treatment method in oncology.

The classical effect is based on well-focused energy absorption targeting the malignant tissue.

Unfortunately, the heat-shock protein (HSP) synthesis may considerably suppress the treatment's efficiency, causing cells to adapt and survive the shock. Electro-hyperthermia heats the targeted tissue by means of electricity, producing less HSP in the cells than classical hyperthermia.

The main improvement is keeping the energy absorption within the extracellular matrix (ECM). By heating the ECM, ion-mobility increases, metabolic rates increase, and the heat destroys the cells' membrane before the heat-shock activates the intra-cellular HSP mechanisms.

1. Introduction

There are intensive discussions in scientific communities on the mechanism of oncological hyperthermia. The number of conferences and journals on the subject has escalated.

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. Some of these are summarised below.

Localization	Convent. response [%]	Adjuvant hyperthermia resp. [%]	Ref:
Head- and neck CA	15	20	[1]
Cervical CA	52.6	83.3	[2]
Cervical CA	50	80	[3]
Esophagel CA	24.2	50.4	[4]
Malignant melanoma	28	46	[5]
Gastric Tu	35.5	57.6	[6]
Breast CA (superf.)	41	61	[7]
Glioblastoma mf.	15	31	[8]
Superficially located CA	62.6	82.8	[9]
Nonsmall Lung CA	20	73	[10]
Esophagel CA	59	81.2	[11]
Bladder, Cervical, Rectal CA	39	55	[12]

2. Effects of Hyperthermia

Some well-established milestones can help summarize the effects of hyperthermia:

1. At the increase of the temperature, the blood supply of tumors decreases while that of healthy tissue increases. [13].
2. As the metabolism of tumors is very intensive, it is usually warmer than healthy tissues. [14].
3. There is not enough oxygen available for the metabolism of malignant tissues; resulting in hypoxia and anaerobe metabolism, which in turn produces acidosis. [15].
4. Increased metabolism significantly depletes the ATP stores of the cells, resulting in increased apoptosis. [15].
5. DNA replication can often be blocked by heat, therefore slowing down cell division. [16].
6. Hyperthermia complements ionizing radiation:

Effect/Method	Ionizing radiation acts	Hyperthermia acts
Cell cycle	in M+G_1 phase	in S phase
pH-dependence	in alkaline tissues	in acidic regions
Oxygenation	in well oxygenated	in hypoxic tissue

7. The chemo-therapies also can be complemented by hyperthermia

Effects/Method	Chemo-therapy	Hyperthermia
Cell cycle	acts in $M+G_2$ phase	acts in S phase
Chemo penetration	low penetration, due to high pressures	improved penetration by electro osmosis
Chemo metabolism	weak metabolism	good metabolism
Place of activity	acts at arteries	acts far from arteries
Reaction rate	low reaction rate	enhanced reaction rate
Activity	often no effect in G_0	eliminates the G_0 phase

8. Hyperthermia has significant pain-reduction and few side effects. [17].
9. Hyperthermia enhances the efficiency of the immune system [16].

3. Heat Shock Protein Production

HSPs (stress- or heat-shock-proteins) are highly conserved proteins, which are vital in almost every living cell [18]. Stresses activate their synthesis [19], and HSPs help cells accommodate to new challenges. HSPs are present in all cancerous cells helping them to adapt to stresses and help tumor-cells survival. Moreover HSPs are induced by all treatments. This generally provides effective protection of the cells against apoptosis [20] and can lead to a multi-drug resistance [21].

4. Electro-Hyperthermia

Electro-hyperthermia is devoted to enhance the efficiency of conventional hyperthermia by additional, mainly thermally induced, non-thermal effects, and the aim of suppressing the existing disadvantages of classical thermal treatments. Its advantage is that electrically-coupled energy of certain frequencies are primarily absorbed in the ECM, as it is not able to penetrate through the membrane (Fig.1.).

The temperature gradient from the ECM to the cell creates a tremendous heat-flow (1500 nW/mm^2) through the membrane. This is well above the natural metabolic heat-flow of 20 nW/mm^2. Moreover, the high temperature gradient (1 K/mm) forces membrane currents of approximately 150 pA/mm^2, which is dominantly caused by

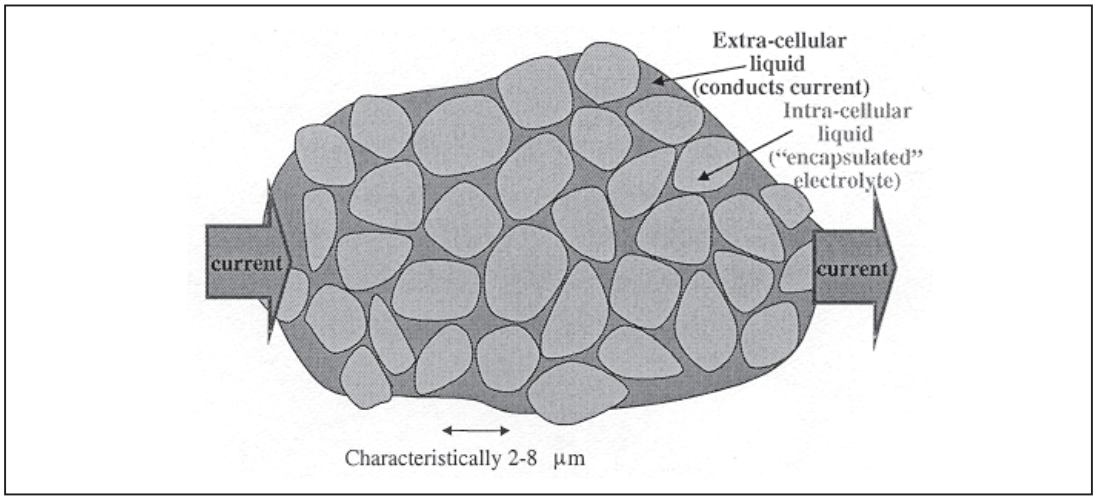

Fig.1. The RF current flows extracellularly

Na^+ influx. In addition, the thermal flux increases intracellular pressure to 1.32 MPa. The membranes of a significant percent of malignant cells are rigid [22], and cannot protect against this increased pressure.

These processes lead to the cell membrane damage of the malignant cells before the heat reaches the cell-nuclei, and could induce HSP synthesis and adaptation to the new stress. However, membrane HSPs are induced by the extreme heat at the membrane. These support apoptotic signals and help eliminate the malignant cells in a natural fashion.

The developed system is technically and medically certified by the European Standards according to the Medical Device Directive.

5. Conclusions

Hyperthermia is one of the effective modalities in oncology. Its improved version, electro-hyperthermia, is highly selective, gentle and safe, providing all the positive effects of classical hyperthermia with the additional advantages of:

1) reobtained apoptotic signal,
2) blocked angiogenesis,
3) blocked HSP synthesis within the cell, thus no heat tolerance or other shock resistance can develop.

The successful operation of electro-hyperthermia systems is in progress in various clinics and hospitals.

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