P-20: Gyula P Szigeti, Gabriella Hegyi, Oliver Szasz (2012) Hyperthermia versus Oncothermia: cellular effects in cancer therapy

Hyperthermia versus Oncothermia: Cellular effects in cancer therapy

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ABSTRACT

Hyperthermia means overheating of the living object completely or partly. Hyperthermia, the procedure of raising the temperature of a part of or the whole body above normal for a defined period of time, is applied alone or as an adjunctive with various established cancer treatment modalities such as radiotherapy and chemotherapy. The fact the hyperthermia is not generally accepted as conventional therapy. The problem is its controversial performance. The controversy is originated from the complications of the deep heating and the focusing of the heat-effect. The idea of oncothermia solves the selective deep action on nearly cellular resolution.

We would like to demonstrate the force and perspectives of oncothermia, as a highly specialized hyperthermia in clinical oncology. Our aim is to prove the ability of oncothermia to be a candidate to become a widely accepted modality of the standard cancer-care. We would like to show the proofs and the challenges of the hyperthermia and oncothermia applications to provide the presently available data and summarize the knowledge in the topic. Like many early-stage therapies, oncothermia lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications.

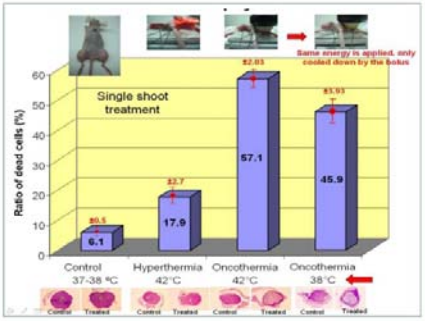

Figure 1.
The cell-destruction ability of oncothermia is three-times higher than hyperthermia at the same 42°C temperature. Pumping the same energy as for temperature 42°C, but cooling the lesion by outside water-bolus (to 38°C temperature), the efficacy of the cell-destruction remained much higher in oncothermia than in hyperthermia at 42°C temperature.

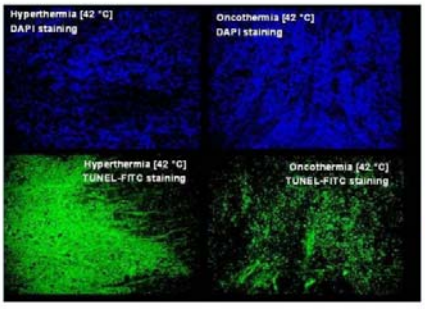

Figure 2.
Upper panel: DAPI staining (stains the double strains of DNA only), lower panel TUNEL-FITC staining (enzymatic label of the strain-break of the DNA).

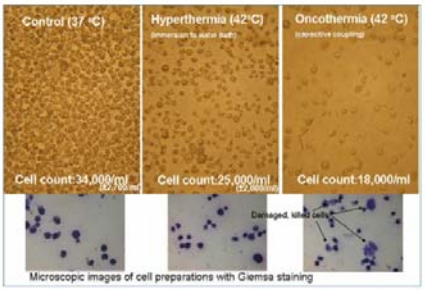

Figure 3.
Comparison of cell death induced by oncothermia with traditional hyperthermia (*in vitro* experiments with fixed sample): HL-60 leukaemia cell line.

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The concept of hyperthermia

The effectiveness of hyperthermia treatment is related to the temperature achieved during the treatment, as well as the length of treatment and cell and tissue characteristics. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumour and surrounding tissues is monitored throughout the hyperthermia procedure. The goal is to keep local temperatures under 44°C to avoid damage to surrounding tissues, and the whole body temperatures under 42°C, which is the upper limit compatible with life.

Mechanisms induced by hyperthermia:

- *Hyperthermia induced cell killing*
  It has been long recognized that hyperthermia in the 40–47°C temperature range kills cells in a reproducible time and temperature dependent manner. In the hyperthermic region there are three cellular responses for thermal therapy: *cytotoxicity, radiosensitization and thermotolerance.*
  The intensity of cell death in hyperthermia is showed cell cycle dependence. Both S- and M-phase cells undergo a 'slow mode of cell death' after hyperthermia. Cells during G1-phase may follow a 'rapid mode of death' immediately after hyperthermia.
- *Vascular*
  With higher heat temperatures there is a corresponding decrease in oxyhaemoglobin saturation, and these changes will result in a decrease in overall oxygen availability. This lack of oxygen will also give rise to a decrease in tumour pH and ultimately lead to ischemia and cell death. Normal tissues typically show a very different vascular response to heat, with flow essentially increasing as the temperature increases.
- *Cellular and intracellular mechanisms of thermal effects in the hyperthermia - Cell metabolism: hypoxia, pH, ATP and its consequences*
  Summarising the relevant data, it can be stated that tumour temperatures >42.5°C and appropriate heating can reduce both intracellular and extracellular pH, which may further sensitise tumour cells to hyperthermia in the sense of a positive feedback mechanism. Relevant pathogenetic mechanisms leading to an intensified acidosis upon heat treatment (which is reversible after hyperthermia) are:
  1. an increased glycolytic rate with accumulation of lactic acid,
  2. an intensified ATP-hydrolysis,
  3. an increased ketogenesis with accumulation of acetoacetic acid and β-hydroxybutyric acid,
  4. an increase in CO_2 partial pressures,
  5. changes in chemical equilibria of the intra- and extracellular buffer systems, and
  6. an inhibition of the Na^+/H^+ antiporter in the cell membrane.

  The ATP decline observed upon heat treatment is mostly due to
  1. an increased ATP turnover rate (i.e. intensified ATP hydrolysis). As a result of an increased ATP degradation, an accumulation of purine catabolites has to be expected together with a formation of H^+ ions and reactive oxygen species at several stages during degradation to the final product uric acid,
  2. a poorer ATP yield as a consequence of a shift from oxidative glucose breakdown to glycolysis.
- *Effects on proteins that contribute to resistance to other stresses, for example, DNA damage*
  At higher temperatures, inhibition of HSP-synthesis occurs above a distinct threshold temperature. In general, the temperature, respectively, thermal dose at which HSP synthesis is inhibited in a given experimental system varies between different cell types, but the respective threshold can be lowered when further (proapoptotic) stimuli are added. As lack of HSP-synthesis is associated with exponential cell death, it is generally accepted that HSPs prevent cells from lethal thermal damage. Recently, an additional role has been ascribed to HSPs which should be importance in hyperthermia as activators of the immune system.

Problems with hyperthermia

The high energy application could cause controversies: the high temperature burns the malignant cells but it's missing selectivity. The healthy cells are damaged also and the hyperthermia starts unwanted physiological reactions as well as enlarged dissemination possibility. These conditions make the hyperthermia effect not controlled.

Change of Paradigm - The concept of oncothermia

Oncothermia technology heats non-equally: concentrating the absorbed energy to the intercellular electrolytes. This method creates inhomogeneous heating, microscopic temperature differences far from thermal equilibrium. The definitely large temperature gradient between the intra- and extracellular liquids changes the membrane processes, ignites signal pathways for natural programmed cell-death, avoiding the toxic effects of the simple necrosis.

Mechanisms induced by oncothermia

- *Oncothermia promotes the programmed cell-deaths of tumor*
  Detecting the double strains of DNA (DAPI staining, see *Figure 2.* upper panel) and measuring the enzymatic labeled strain-breaks of DNA (TUNEL-FICT, see *Figure 2.* lower panel) the apoptosis is highly likely in oncothermia. Consequently the main effect in oncothermia is the apoptosis contrary to the conventional hyperthermia, which operates mainly by necrosis. Investigating the apoptosis by various methods (morphology, beta-catenin relocation, p53 expression, Connexin 43, Tunel, DNA-laddering etc.) the effects are indicating the same apoptotic process. This process is non-toxic (no inflammatory reactions afterwards) and promotes the immune reactions and not makes processes against those.
- *Oncothermia limits the dissemination of malignant cell*
  Oncothermia blocks the tumor cell dissemination, avoid their motility due to the lazy connections to the tumor. Oncothermia makes it by the reestablishing the cellular connections, which is also great success to save the life. The built up connections could force not only the sticking together, but makes bridges between the cells for information exchange to limit the individuality, the competitive behavior of the malignant cells.
  These are high efficacy factors favor oncothermia over its temperature-equivalent hyperthermia counterpart, see *Figure 3.* It also produces higher concentration of HSPs in the outer membrane and in the extracellular matrix. The higher HSP concentration in the vicinity of the malignant cells together with the changes of the adherent connections between the cells induces apoptosis.