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Apoptosis induction with modulated radiofrequency (RF) hyperthermia (oncothermia) in immuno-defficient mice xenograft tumors (Review)

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Introduction: Oncothermia method is more than twenty years serves the cancer treatments demands. It is successfully applied both in monotherapy and as complementary therapy with other oncotherapeutic modalities, irrespective their specialties. The experimental preclinical research started five years ago to investigate the theoretically predicted mechanisms by rigorous basic science approvals. The complexity and interdisciplinary of the in vivo experimental series requested a wide cooperative scheme of various respected and honored research institutes and university laboratories. Our objective is to summarize the results of this intensive work and show the conclusions at the recent phase of the investigations.

Method: Immuno-defficient nude mice (BalbC/nu/nu) were used for xenograft and allograft models with HepG2, PC3, HT29, A431, GL261 cell-lines. The definite amount of cell-line suspension was injected to the femoral region of the 6-8 weeks old female mice and after started the oncothermia treatment after 18-20 days, when the tumors were developed symmetrically in both sides on diameter 1-1.5 cm. The single shoot treatment was identically performed for all the mice on their right lesion, while the left lesion was kept as untreated individual control to reduce the inaccuracies due to the individual variability of the animals. Slides of the paraffin-fixed samples were studied by standard HE and by special immuno-hystochemical as well as fragmented (apoptotic) DNA-marking staining. Their structure images were examined by special digital microscopy (PanoramicView, 3DHISTECH, Budapest). Special software made possible various qualitative and quantitative studies of the tissue-morphology facilitating the precise, molecular-based comparison of the efficacy of different therapies.

Treatments were performed by highly specialized laboratory equipment (Lab-EHY, Oncotherm), optimized on mice dimensions, taking into account the physiology of the small animals, collecting all the important technical and biological parameters [1]. The impedance selection and automatic focusing which is well known in human clinical practices were applied in these experiments too [2].

A few sequences were steadily investigated in our program:

1. Qualitatively studied the effect on various animal models.
2. Qualitatively and quantitatively compared oncothermia effect on tumor tissue with the classical heating (hyperthermia) in identical temperature taking attention on the dynamic stress effects also.
3. Studied the development of the tumor by molecular morphological and immuno-histochemical methods in the elapsed time from the single shoot treatment.

Results: Investigations of the time-development of the tumors shown:

1. Oncothermia had induced a certain and significant distortion of malignant-cells in all the allograft and xenograft models compared to their own control tumors. The healthy tissues around the tumors had no effect, their remained intact in both sides (treated and control) of the animals.
2. The high promotion (~70-100 %) of the efficacy of the studied chemotherapies (e.g. MMC) was observed.

3. The constricted RF-current rearranged the ionic structure of the extracellular electrolyte, rearranging the adherent connections (E-cadhetin, beta-catenin, p120 catenin). These reconnected connections probable promote or ignite some signal-transductive pathways to destroy the malignant cells, [3].
4. Both the classical heating (hyperthermia) and the modulated electro-heating (oncothermia) have significant tumor-destructive capability in the studied model, however the oncothermia is approx. three-times more efficient [4].
5. On the basic of the well documented tumor-destruction (measured by immuno-histochemical and TUNEL experiments) is dominantly apoptotic and accompanied by considerable leukocyte infiltration. The observed phenomenon allows the possibility of the role of p53 tumor-suppressor gene in these processes.

Conclusion: The applied mice models were suitable to study the effect of oncothermia on molecular level. The dominant role of apoptosis in the oncothermia cell-destruction is highly probable. Further investigations are in progress to study the mechanism of apoptotic induction and its connection with the leukocyte infiltration as well as the role of the adherens and other cellular connections.

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