Oncothermia and beyond

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Background: Modulated electro-hyperthermia (mEHT, oncothermia) is a non-invasive technique for targeted tumor treatment. The oncothermia generated capacitive impedance-coupled modulated radiofrequency selectively accumulates in the tumor tissue without major effect in the surrounding normal tissues. Research *in vitro*, *in vivo* and in veterinarian practice have been performed for studying the underlying mechanism of action of oncothermia. Also, human clinical studies in large number of patients with advanced cancer have been done in combination with conventional therapies. Our aim is to briefly sum up experimental and clinical evidences on oncothermia in cancer treatment.

Method: In the *in vivo* experiments HT29 human colorectal carcinoma cell line was xenografted into both femoral region of BalbC/nu/nu mice. A single shot oncothermia treatment (LabEHY, Oncotherm Ltd, Hungary) for 30 minutes was performed when the xenografts reached ~1.5 cm. Sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, 216 h in 3 mice each group by keeping 5 untreated animals. Histomorphologic, immunhistochemical and TUNEL assay results were tested in digital slides and analyzed semi-quantitatively. The R&D Proteome profiler Human Apoptosis Arrays were also used and evaluated using the ImageJ software. The clinical studies involved retrospective and prospective mostly in higher (third or subsequent) treatment lines either as supplementary or monotherapy. Treatment data gained from different clinics were compared in relation to the same localization and protocols used. Survival data involving oncothermia were correlated with large databases using traditional therapy modules as extracted from SEER (US database) and Eurocare (European database).

Results: In invasive colorectal cancer xenografts oncothermia caused programmed cell death by starting cell destruction from the tumor centre. TRAILR2 and FADD apoptosis receptor proteins and some of their related downstream pro-apoptotic regulatory proteins (Bax, SMAC/Diablo and HTRA2/Omi)were upregulated 8h post treatment. However, cleaved/activated caspase-3 positive cells appeared only at the tumor periphery between 4-14h. As further signs of apoptosis cytochrome-c release from mitochondria to the cytoplasm between 8-14h post treatment, and nuclear translocalisation of AIF between 14-24h were observed. Massive TUNEL positivity 24-48h post-treatment indicated DNA fragmentation. At 72-216h myeloperoxidase positive and CD3 positive leukocyte infiltration ring supported tumor elimination. In clinical studies involving brain gliomas, pancreas adenocarcinomas and colorectal carcinomas metastatic to the liver- the 12-month survival data were . In general, the efficacy of treatment involving oncothermia significantly exceeded that of traditional treatment modalties as found in public databases.

Conclusion: Oncothermia can be a successful treatment cancer in combination with conventional therapies. In HT29 colorectal cancer xenograft oncothermia caused programmed cell death. DNA fragmentation followed a caspase independent and AIF dependent subroutine.