HYPERTHERMIA ENHANCES ANTI-ANGIOGENIC EFFECT OF MANGANESE PORPHYRIN MIMETIC OF SUPEROXIDE DISMUTASE

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Purpose. The objective of our study was to determine the effect of hyperthermia (41°C) combined with MnTE-2-PyP5+, a manganese porphyrin mimetic of superoxide dismutase with anti-angiogenic properties, on tumor growth delay and angiogenesis in murine melanoma tumors.

Methods and Results. C57/B6 mice with B16F10 melanoma tumors implanted on the right flank were randomized into 4 groups (n=8/each): control (saline), MnTE-2-PyP5+ alone, hyperthermia alone, or hyperthermia with MnTE-2-PyP5+. MnTE-2-PyP5+ (5mg/kg) was delivered subcutaneously BID for the duration of the experiment. Mice were exposed to localized hyperthermia to the right flank a total of three times for 1 hr each at 41°C. Tumors were harvested at sacrifice and animals were examined for lung and other organ metastasis. Tissue sections were stained for HIF-1α and VEGF. Animals treated with MnTE-2-PyP5+ alone, hyperthermia alone, and with combined therapy exhibited a substantial delay in tumor growth when compared to the saline control (p<0.05). Tumor growth was most inhibited in the group receiving combined therapy (MnTE-2-PyP5+ and HT). Preliminary assessment of angiogenic activity revealed HT and MnTE-2-PyP5+ combination was the most effective in inhibiting HIF1α and VEGF immunoreactivity.

Conclusions. Our data show hyperthermia has an enhanced effect on tumor growth delay when given in combination with anti-angiogenic therapy. Furthermore, the mechanism of tumor growth delay may be attributable to impaired angiogenesis consistent with decreased HIF1a stabilization and transcriptional activity of the potent angiogenic factor, VEGF. In addition to the above histological staining, we are continuing to investigate the mechanism behind HT mediated tumor growth delay. Currently, we are investigating changes in microvessel density (CD31), macrophages (ED-1), oxidative stress (8-OHdG), and hypoxia (CA9) between the control and treatment groups.