The purpose of this study was to investigate the use of IONP in combination with fractionated ionizing radiation, with and without magnetically induced mild localized hyperthermia, to enhance conventional fractionated radiation. It has been shown that ionizing radiation combined with hyperthermia can result in a greater therapeutic ratio than radiation or hyperthermia alone. Recent work has also shown that iron oxide nanoparticles may have potential as radiation sensitizers. IONP are additionally interesting because when IONP are exposed to an alternating magnetic field (AMF), a localized hyperthermia can be induced. In 1977 Adams et al. published a study which showed enhanced radiation-induced lymphocyte toxicity caused by the iodine (contrast agent) in angiotherapy patients. Since then, the body of materials shown to modify the toxicity of radiation has grown, including not only high-Z materials, but also nanoparticles, which also showed enhanced radiation-induced lymphocyte toxicity caused by the iodine (contrast agent) in angiotherapy patients.4 While IONP are just beginning to be investigated as ionizing radiation sensitizers, significant research has been conducted to develop IONP-AMF mediated hyperthermia as a primary or adjuvant cancer therapy. Physiologically meaningful changes due to the combination of mild heat and radiation have been demonstrated in numerous cancer studies using a wide variety of heating techniques (microwave, ultrasound, perfusion and regional/whole body). Previous studies, have shown that raising the temperature of tumors with IONP-mediated hyperthermia can potentiate the efficacy of ionizing radiation.9,10 However, these studies have not considered the interaction of the IONP themselves with the ionizing radiation or as part of a fractionated treatment plan.

Methods: Murine mammary adenocarcinoma (MTGB) tumors were grown in C3H mice. Six groups were utilized, including two control groups: IONP alone and phosphate buffered saline (PBS) injection alone. Tumors treated with radiation (5 X 3 Gy) were compared to those receiving the same radiation dose with intratumoral injections of IONP (7.5 mg Fe/g tumor). Additional treatment groups included IONP induced hyperthermia (2 X 43°C for 30 minutes) with and without radiation. Treatment outcome was measured by tumor regrowth.

Results: On average, control mice reached the study endpoint at 7 days (SD 2.4) after the initiation of treatment. Mice which received IONP alone, showed regrowth at an average of 8 days (SD 1.8). IONP, without ionizing radiation or AMF (heat) did not significantly alter the tumor growth kinetics (p=0.48). IONPH demonstrated modest therapeutic improvement over control mice with an average regrowth of 11 days (SD 2.3, p=0.01). Radiation (no IONP) did not significantly alter tumor growth with an average regrowth of 9 (SD 3.3, p=0.16). When IONP was included in the radiation scheme, tumor regrowth was significantly improved compared to ionization radiation alone (average 16 days, SD 6.6, p = 0.02). Mice which received IONPH combined with radiation demonstrated the greatest regrowth delay. Of the seven mice treated with IONPH + Rad, one mouse was tumor free after six months. Of the remaining six mice, the average regrowth time was 25 days (SD 7.7). This represents a 3.3X improvement compared to the control mice with an average regrowth of 11 days (SD 2.3, p=0.01). Radiation (no IONP) did not include AMF exposure received comparable probe placement, core temperature maintenance, and anesthesia. The CEM was used to prescribe the thermal dose (43°C for 30 minutes). Groups which did not include AMF exposure received comparable treatment plans, core temperature maintenance, and anesthesia. The CEM was used to prescribe the thermal dose. The CEM relationship relates the biologic effect of a thermal probe in terms of equivalent minutes at 43°C and is specific to cell/tissue type, as well as other physiologic conditions.

Conclusions: This study indicates that IONP may significantly improve the therapeutic efficacy of fractionated ionizing radiation in a clinical setting as a monotherapy, or in an adjuvant approach with mild AMF-induced hyperthermia. The mechanism of sensitization is not yet determined, but is likely a physical or chemical (ROS) effect, which is improved by the induced mild hyperthermia.

Citations: