Iron oxide nanoparticle enhancement of ionizing radiation cancer therapy

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Introduction: 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.[1] Recent work has also shown that iron oxide nanoparticles may have potential as radiation sensitizers.[2] 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 angiocardiography patients.[3] 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 may act as carriers for pharmacologic agents. These materials may the reverse radiation resistance, enhance sensitivity, or provide radioprotection of normal tissue.[2] Though largely unexplored, a proposed mechanism for radiation sensitization by IONP includes the increase in production of reactive oxygen species (ROS) when ionizing radiation interacts with IONP.[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.[5,6] 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).[7,8] 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.

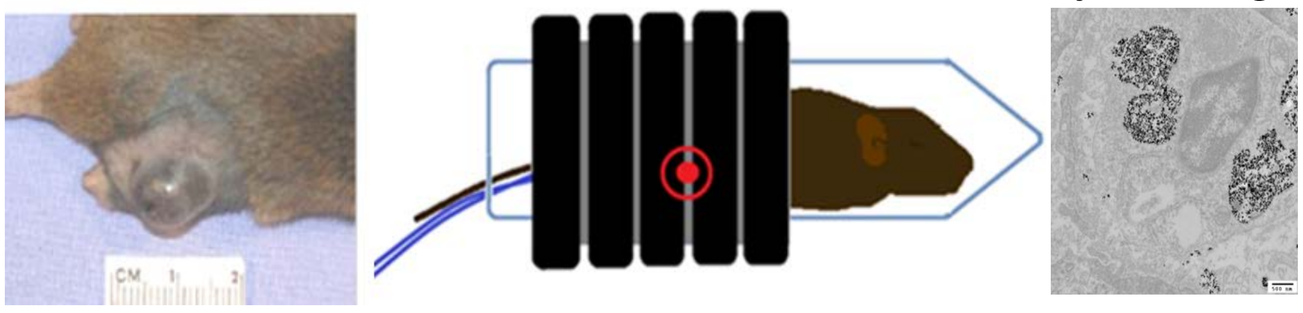

Figure 1: Left to right, C3H/MTGB flank tumor, location of flank tumor with fiber optic temperature probes in AMF coil, TEM image of IONP in MTGB cell 4 hours after injection, treatment plans for experimental groups.

Model: Flank tumors were grown in female C3H mice (The Jackson Laboratory, Bar Harbor, ME) following inoculation with syngeneic MTGB cells. IONP injection, radiation, AMF exposure and the corresponding sham treatments, were all performed under 1-3% isoflurane gas and 95% O_2. Control injections utilized PBS at the prescribed IONP volume. Animal experiments were approved by the Dartmouth College Institutional Animal Care and Use Committee, in accordance with all federal, institutional and Association for Assessment and Accreditation of Laboratory Animal Care guidelines. NT-01 particles (micromod Partikeltechnologie GmbH, Germany), are composed of magnetite and clinical grade dextran (MW = 40,000 Da). The magnetite core is made up of multiple crystals with single magnetic, monocrystalline domains, each 20 to 25 nm in diameter.
Radiation: Mice were irradiated under anesthesia using a clinical Varian linear accelerator (Palo Alto, CA). Control groups received comparable transportation to suite and anesthesia.
AMF System and Thermometry: IONP hyperthermia was induced by exposing the IONP to an AMF generated by a whole body coil.[11] The mice were placed inside a plastic tube which served both as means of administering anesthesia and to shield the mice from the direct air flow of the ambient temperature modulation system, maintaining normal physiologic temperatures. Fiber optic probes and accompanying software were used to prescribe the thermal dose to the tumor, as well as maintaining normal physiologic core temperature (FISO fiber optic probes and FISO Evolution software, FISO Inc., Quebec, Canada). A probe was placed in the center of the tumor to prescribe the thermal dose (43°C for 30 minutes). Groups which did not include hyperthermia also had temperature probes placed in their tumors. A probe was also placed in the rectum to monitor core temperatures. Groups which did not include AMF exposure received comparable probe placement, core temperature maintenance, and anesthesia. The CEM was used to the prescribe the thermal dose. The CEM relationship relates the biologic effect of a thermal history in terms of equivalent minutes at 43°C and is specific to cell/tissue type, as well as other physiologic conditions.[12]

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 ionizing 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 at 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 IONP alone (p=0.0019), 2.3X compared to IONPH alone (p=0.0053), 1.6X compared to ionizing radiation with IONP (p=0.039) and 2.8X compared to radiation without IONP (p=0.0024).

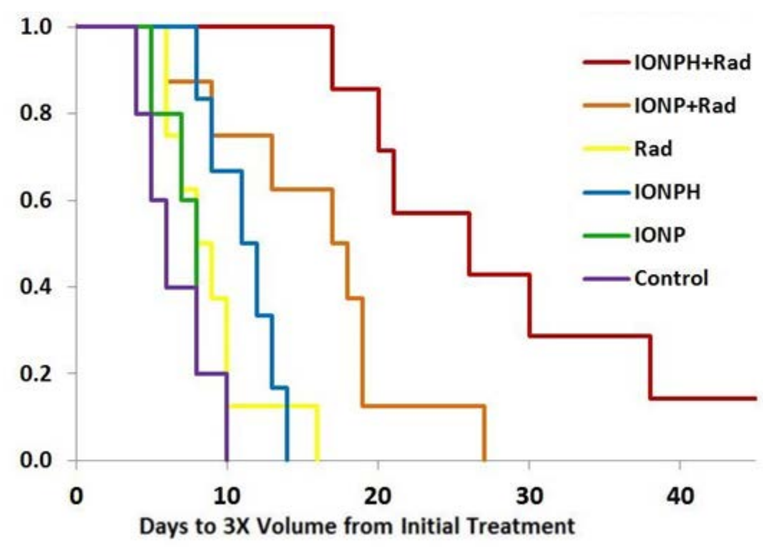

Figure 2: Kaplan-Meier "survival curve," with the number of days to 3X initial tumor volume as study endpoint

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

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