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Radioprotective Effects of Super-Paramagnetic Iron Oxide Nanoparticles Used as Magnetic Resonance Imaging Contrast Agent for Magnetic Resonance Imaging-Guided Radiotherapy

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Abstract : Background. Visibility of hepatic malignancies is poor on non-contrast imaging for daily verification of liver malignancies prior to radiation therapy on MRI-guided Linear Accelerators (MR-Linac). Ferumoxytol® (Feraheme, AMAG Pharmaceuticals, Waltham, MA) is a SPION agent that is increasingly utilized off-label as hepatic MRI contrast. This agent has the advantage of providing a functional assessment of the liver based upon its uptake by hepatic Kupffer cells proportionate to vascular perfusion, resulting in strong T1, T2 and T2* relaxation effects and enhanced contrast of malignant tumors, which lack Kupffer cells. The latter characteristic has been recently utilized for MRI-guided radiotherapy planning with precision targeting of liver malignancies. However potential radiotoxicity of SPION has never been addressed for its safe use as an MRI-contrast agent during liver radiotherapy on MRI-Linac. This study defines the radiomodulating properties of SPIONs in vitro on human monocyte and macrophage cell lines exposed to 60Go gamma-rays within clinical radiotherapy dose range. Methods. Human monocyte and macrophages cell line in cultures were loaded with a clinically relevant concentration of Ferumoxytol (30μg/ml) for 2 and 24 h and irradiated to 3Gy, 5Gy and 10Gy. Cells were washed and cultured for additional 24 and 48 h prior to assessing their phenotypic activation by flow cytometry and function, including viability (Annexin V/PI assay), proliferation (MTT assay) and cytokine expression (Luminex assay). Results. Our results reveled that SPION affected both human monocytes and macrophages in vitro. Specifically, iron oxide nanoparticles decreased radiation-induced apoptosis and prevented radiation-induced inhibition of human monocyte proliferative activity. Furthermore, Ferumoxytol protected monocytes from radiation-induced modulation of phenotype. For instance, while irradiation decreased polarization of monocytes to CD11b+CD14+ and CD11bnegCD14neg phenotype, Ferumoxytol prevented these effects. In macrophages, Ferumoxytol counteracted the ability of radiation to up-regulate cell polarization to CD11b+CD14+ phenotype and prevented radiation-induced down-regulation of expression of HLA-DR and CD86 molecules. Finally, Ferumoxytol uptake by human monocytes down-regulated expression of pro-inflammatory chemokines MIP-1α (Macrophage inflammatory protein 1α), MIP-1β (CCL4) and RANTES (CCL5). In macrophages, Ferumoxytol reversed the expression of IL-1RA, IL-8, IP-10 (CXCL10) and TNF-α, and up-regulates expression of MCP-1 (CCL2) and MIP-1α in irradiated macrophages. Conclusion. SPION agent Ferumoxytol increases resistance of human monocytes to radiation-induced cell death in vitro and supports anti-inflammatory phenotype of human macrophages under radiation. The effect is radiation dose-dependent and depends on the duration of Feraheme uptake. This study also finds strong evidence that SPIONs reversed the effect of radiation on the expression of pro-inflammatory cytokines involved in initiation and development of radiation-induced liver damage. Correlative translational work at our institution will directly assess the cyto-protective effects of Ferumoxytol on human Kupfer cells in vitro and ex vivo analysis of explanted liver specimens in a subset of patients receiving Feraheme-enhanced MRI-guided radiotherapy to the primary liver tumors as a bridge to liver transplant.

Keywords : superparamagnetic iron oxide nanoparticles, radioprotection, magnetic resonance imaging, liver
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