MRI-guided Focused Ultrasound-Mediated Drug Delivery to Pancreatic Cancer: Safety and Efficacy

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Introduction

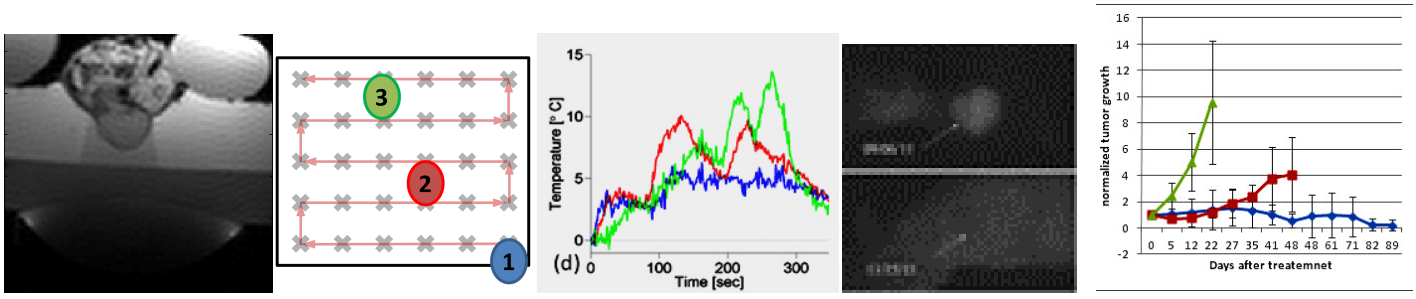
During the last decade, magnetic resonance imaging guided, focused ultrasound-mediated drug delivery (MRgFUS) has attracted attention as an efficient means of drug targeting to tumors. Ultrasound triggers drug release from carrier and increases drug extravasation and deposition in tumor cells. In the current study, this approach was used for treating pancreatic cancer that presents the toughest challenge for chemotherapy. The drug (paclitaxel) was encapsulated in the ultrasound-responsive nanocarrier, perfluorocarbon nanoemulsion. Fluorine magnetic resonance spectroscopy (^{19}F MRS) was used to monitor drug carrier biodistribution. MR thermometry was used to control ultrasound treatment.

Methods

Red Fluorescence Protein (RFP) transfected MiaPaCa-2 tumors were subcutaneously grown in nu/nu mice. Paclitaxel (PTX)-loaded perfluorocarbon nanodroplets were formed by perfluoro-15-crown-5-ether (PFCE) and injected systemically. The tumor was treated with MRgFUS 6 to 8 hours after the drug injection. A small animal 3-MHz HIFU device (IGT, Inc.) generated a 1 x 2 mm ultrasound focal spot and all treatments were performed in a Siemens Trio 3T MRI. The temperature rise in the tumor was measured by MRI thermometry using a 2D GRE segmented EPI sequence. A single treatment was given and only a fraction of the total tumor volume was treated, analogous to a worst clinical scenario. Cancer cell death was monitored by RFP imaging.

Results and Discussion

A single combined tumor treatment with MRgFUS at 1.5 W or 2.1 W and PTX-loaded PFCE nanodroplets resulted in a significant delay of tumor growth, dramatic survival benefit, and, in several cases, complete resolution of pancreatic cancer. Application of MRgFUS without any injection had no effect on the tumor growth while MRgFUS treatment combined with empty (i.e. not drug loaded) nanodroplets manifested a detrimental effect that was presumably caused by the enhanced tumor perfusion and/or tissue inflammation that counteracted the effect of treatment and accelerated tumor growth. The data suggested that under ultrasound, drug was “splashed” from the sonicated volume throughout the tumor tissue. Application of ultrasound at higher power levels was less effective, which was presumably associated with the enhanced tumor perfusion. In addition, pre-treatment MR images revealed the injurious effect of intestinal gases that was presumable caused by ultrasound reflection and formation of standing waves that resulted in the intestinal damage.



Left to right: sagittal image of a mouse in a magnet; grid trajectory of ultrasound beam; temperature rise curves at the points 1, 2, and 3; complete resolution of the fluorescent pancreatic tumor; tumor growth curves: green – control; red – treatment with PTX-loaded nanodroplets without MRgFUS; blue – combined nanodrug/MRgFUS treatment.

Conclusions

Even a single treatment of the fraction of the pancreatic tumor with the MRgFUS and nanodroplet-encapsulated drug may result in a significant delay of pancreatic tumor growth or complete tumor resolution.