Image-Guided Drug Delivery to Tumors using Ultrasound-Activated Perfluorocarbon Nanoemulsions as Drug Carriers

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Background: Many aspects of the mechanisms involved in ultrasound-mediated therapy remain obscure. In particular, the relative roles of drug and ultrasound, the effect of the time of ultrasound application, and the effect of tissue heating are not yet clear. The current study was undertaken with the goal to clarify these aspects of the ultrasound-mediated drug delivery mechanism.

Methods: Focused ultrasound-mediated drug delivery was performed under MRI guidance (MRgFUS) in a pancreatic ductal adenocarcinoma (PDA) model grown subcutaneously in nu/nu mice. Paclitaxel (PTX) was used as a chemotherapeutic agent because it manifests high potency in the treatment of gemcitabine-resistant PDA. Poly(ethylene oxide)-co-poly(D,L-Lactide) block copolymer stabilized perfluoro-15-crown-5-ether nanoemulsions were used as drug carriers. MRgFUS was applied at sub-ablative power levels in both continuous wave and pulsed modes and only a fraction of the tumor was treated.

Results: Positive treatment effects and even complete tumor resolution were achieved by treating the tumor with MRgFUS after injection of nanodroplet encapsulated drug. The MRgFUS

treatment enhanced the action of the drug through enhanced tumor perfusion and blood vessel and cell membrane permeability that increased the drug supply to tumor cells. The effect of the pulsed MRgFUS treatment with PTX-loaded nanodroplets was clearly smaller than that of continuous wave MRgFUS treatment, supposedly due to significantly lower temperature increase as measured with MR thermometry. The time of the MRgFUS application after drug injection also proved to be an important factor with the best results observed when ultrasound was applied at least six hours after the injection of drug-loaded nanodroplets. Some collateral damage was observed with particular ultrasound protocols supposedly associated with enhanced inflammation.

Conclusion: This presented data suggest that there exists an optimal range of ultrasound application parameters and drug injection time. Decreased tumor growth, or complete resolution, was achieved with continuous wave ultrasound powers below or equal to 3.1 W and drug injection times of at least 6 hours prior to treatment. Increased acoustic power or ultrasound application before or shortly after drug injection gave increased tumor growth when compared to other protocols.