MMCM-based MR imaging of tumor vascular response to photodynamic therapy and the antivascular agent, 5,6 dimethyl xanthenone-4-acetic acid

M. Seshadri[1], R. Mazurchuk[2], J. Spernyak[2], D. Bellnier[1]

[1]Cellular Stress Biology - Photodynamic Therapy Center, Roswell Park Cancer Institute and Hospital, Buffalo, NY, United States, [2]Cancer Biology - Preclinical MR imaging resource, Roswell Park Cancer Institute and Hospital, Buffalo, NY, United States

Introduction

Pre-clinical evaluation of combination therapies can provide mechanistic insights into the interactions between the individual treatments and allow optimization for maximal therapeutic benefit. Because it is often difficult or impossible to differentiate direct cell kill effects *in vivo* from primary events associated with vascular damage, the development of non-invasive techniques to serially assess vascular response is critically important. In this study, we utilized MMCM-based MR imaging to assess tumor vascular response to photodynamic therapy (PDT) and the antivascular agent, 5,6-dimethyl xanthenone-4-acetic acid (DMXAA) alone and in combination.

Methods

Measurements were performed on mice with subcutaneously implanted Colon 26 tumors. All images were acquired on using a GE 4.7T/33-cm horizontal bore magnet incorporating AVANCE digital electronics (Bruker Medical, Billerica, MA). Relaxivity measurements of the MMCM (methoxy-PEG succinyl-poly-L-lysine-DTPA: MacroGd^{TM}; PharmIn Ltd) were calculated *in vitro* and correlated to the agent concentration. Vascular permeability was assessed using serially acquired T1-weighted images following MMCM administration. T1-relaxation rates of tumor and normal tissues *in vivo* were calculated as a function of time and treatment.

Results

Both PDT and DMXAA treatments caused a significant increase in permeability over time compared to untreated controls. Tumors treated with either HPPH-PDT (48 J/cm^2 delivered at 14 mW/cm^2: Fig.1A) or high-dose DMXAA (Fig.1B), showed the greatest increases in vascular permeability after 4 hours (Fig.2b,c). Permeability continued to increase following HPPH-PDT, but a reduction in permeability by 45% attributed to vascular shutdown was seen 24 hours after the DMXAA treatment. The combination of ineffective doses of DMXAA and PDT (Fig.1C) also resulted in a significant increase in permeability at 4 hours after treatment. However, as with high-cure rate DMXAA (30 mg/kg), there was a significant decrease (33%) in tumor relaxation rates 24 hours after treatment (Fig.2), which we attributed to the loss of functional tumor vessels. Vascular response to DMXAA alone (a,b,c) and PDT-DMXAA combination (g,h,i) was selective compared to PDT alone (d,e,f), as seen in the T1-relaxation maps (Fig.3).

Discussion

MMCM-based MR imaging provides a valuable tool for optimizing dosing schedule with combination therapies such as DMXAA and PDT based on tumor vascular function. Of particular interest is the potential for MMCM-based MRI to delineate a threshold for complete vascular shutdown as seen with the high-dose of DMXAA. Further studies are now being performed to establish and correlate these vascular changes with the long-term tumor response to treatment.

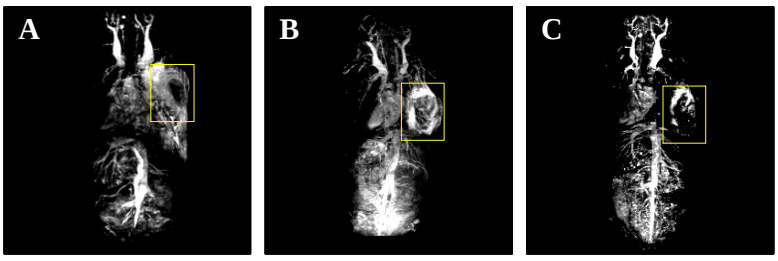

Figure 1

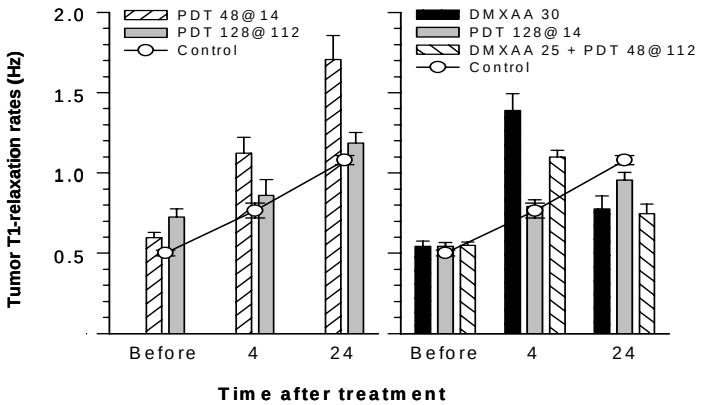

Figure 2

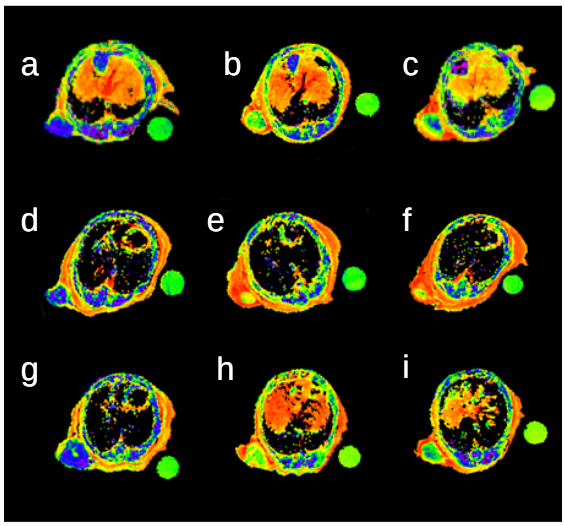

Figure 3