Constrained multi-agent tracer-kinetic modeling to assess tumor vascular changes induced by DMXAA treatment

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Purpose To fully assess the effects of antivascular therapy on tumor vasculature with DCE-MRI, a detailed tracer-kinetic analysis is required. We have previously demonstrated a novel constrained multi-agent tracer-kinetic modeling approach, that enables simultaneous and self-consistent assessment of blood flow and permeability within one imaging session [1]. In the present study, we have applied the multi-agent approach to assess the effects of DMXAA treatment. The main mechanism of vascular shutdown induced by DMXAA is known to be via increased vascular permeability, leading to elevated interstitial pressure and subsequent reduction in blood flow [2]. To assess the potential of the multi-agent DCE-MRI approach, we attempted to identify these effects in a mouse tumor model.

Methods Contrast agents: modified poly(propylene imine) (PPI) dendrimers of generation 2 (G2-PPI-(PEG$_6$-GdDOTA)$_8$) and 5 (G5-PPI-(PEG$_6$-GdDOTA)$_{64}$) were synthesized by SyMO-Chem BV and Gd-DOTA (Dotarem) was purchased from Guerbet. The molecular weights of the G2 and G5 dendrimers and Dotarem are 7317, 59517 and 754 Da, respectively. Evaluation of DMXAA treatment using multi-agent DCE-MRI: CT26 colon carcinoma bearing (hind limb) Balb/c mice (n=3) underwent multi-agent DCE-MRI one day before, 2 h after and 24 h after DMXAA treatment (i.p. injection of 20 mg/kg). MRI was performed with a 7 T Bruker BioSpec 70/30. T_2-weighted imaging was performed for anatomical reference, B_1 mapping was performed based on the 180° signal-null method [3] and pre-contrast T_1 mapping was performed using a variable flip angle approach. Multi-agent DCE-MRI measurements were performed using an RF-spoiled 3D FLASH sequence with the following acquisition parameters: TR = 1.38 ms, TE = 0.69 ms, FA = 15°, acquisition matrix = 50x39x14 (reconstructed to 75x75x16), FOV = 30x30x24 mm^3, temporal resolution = 0.82 s, scan time = 10 min. Contrast agent injections (0.1 mmol Gd/kg) were performed at 1 (G5 dendrimer), 4 (G2 dendrimer) and 7 (Gd-DOTA) min after start of the acquisition, at a rate of 2 mL/min using an infusion pump. ΔR_1 values were calculated based on the signal equation for a spoiled gradient-echo sequence, using the B_1-corrected pre-contrast T_1 values and post-contrast dynamic signal intensities. Multi-agent tracer-kinetic modeling: ΔR_1 curves were scaled by the contrast agent relaxivity, measured in mouse plasma at 7T at 37°C. Arterial input functions (AIFs) were determined for each agent separately using the Monte Carlo Blind Estimation algorithm [4]. Multi-agent data were simultaneously fit with the gamma capillary transit time (GCTT) model [5]. Blood volume (v_b), mean capillary transit time (t_c), vascular heterogeneity index (α^{-1}), interstitial space volume fraction (v_e) and delay time between contrast agent injection and bolus arrival in the tumor (t_d) were constrained to be identical between the boluses, while the extraction fraction (E) was separately assessed for each agent, resulting in 8 free parameters for multi-agent modeling. The blood flow (F) was calculated by $F=v_b/t_c$. No scaling factor for the AIF was obtained yet, which could affect absolute values of F. Median tracer-kinetic parameters were calculated in pixels with significant enhancement after injection of the G5 dendrimer (>2*std pre-contrast). These pixels were regarded as perfused.

Results The blood flow maps in Figure 1A show that both at 2 and 24 h after DMXAA treatment, blood flow was decreased compared to pre-treatment. The decrease in blood flow was accompanied by a clear increase in extraction fraction of the G5 dendrimer at 2 h after treatment, whereas at 24 h after treatment it was decreased again. Representative ΔR_1 curves in a single tumor pixel before and 2 h after treatment are shown in Figure 1B. At 2 h after treatment, the enhancement pattern was markedly different than before treatment, which was reflected by differences in tracer-kinetic parameters (Legend of Figure 1B). Figure 1C-H show the changes in median parameter values for the three mice. The perfused tumor fraction (Figure 1C) was decreased at 2 h after treatment and further decreased at 24 h after treatment. The median blood flow (Figure 1D) in the perfused pixels was reduced both at 2 h and at 24 h after treatment. An increased mean capillary transit time was measured at 2 h after treatment, which remained approximately equal at 24 h. Figure 1F shows that the extraction fraction of the G5 dendrimer strongly increased at 2 h after DMXAA treatment and partially decreased again at 24 h after treatment. A similar pattern was found for the extraction fraction of the G2 dendrimer (Figure 1G), although the increase at 2 h was less pronounced than for the G5 dendrimer. No clear treatment effects on the extraction fraction of Gd-DOTA (Figure 1H) could be seen.

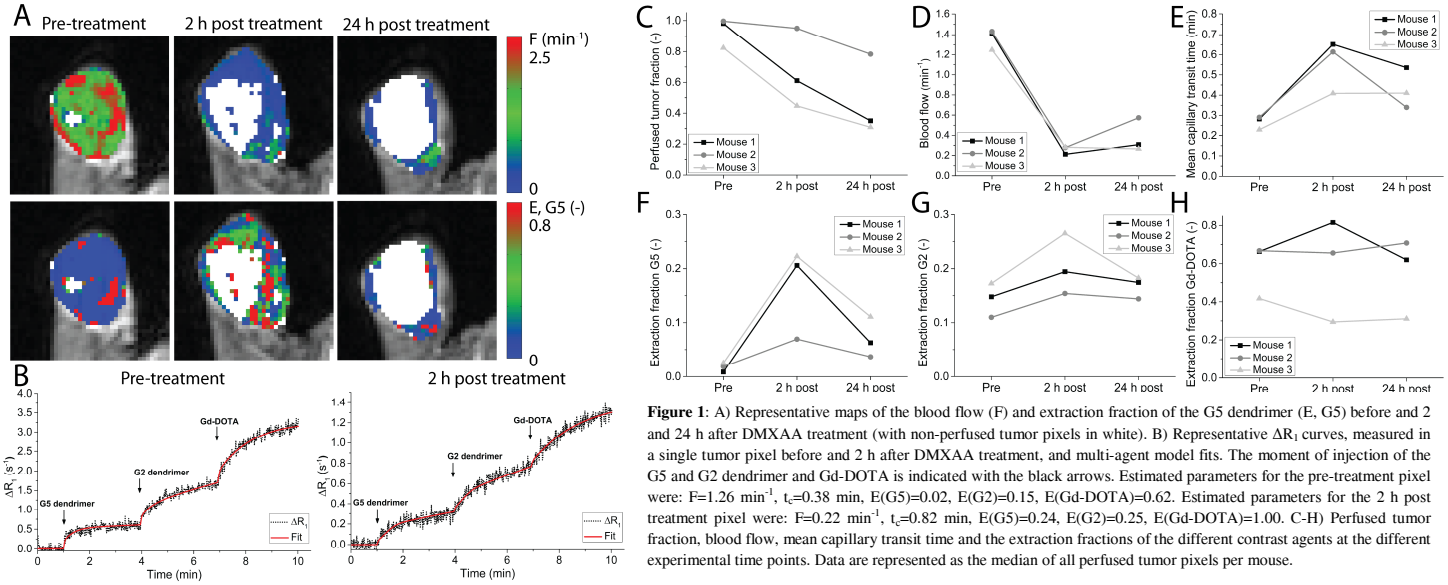

Figure 1: A) Representative maps of the blood flow (F) and extraction fraction of the G5 dendrimer (E, G5) before and 2 and 24 h after DMXAA treatment (with non-perfused tumor pixels in white). B) Representative ΔR_1 curves, measured in a single tumor pixel before and 2 h after DMXAA treatment, and multi-agent model fits. The moment of injection of the G5 and G2 dendrimer and Gd-DOTA is indicated with the black arrows. Estimated parameters for the pre-treatment pixel were: F=1.26 min^{-1}, t_c=0.38 min, E(G5)=0.02, E(G2)=0.15, E(Gd-DOTA)=0.62. Estimated parameters for the 2 h post treatment pixel were: F=0.22 min^{-1}, t_c=0.82 min, E(G5)=0.24, E(G2)=0.25, E(Gd-DOTA)=1.00. C-H) Perfused tumor fraction, blood flow, mean capillary transit time and the extraction fractions of the different contrast agents at the different experimental time points. Data are represented as the median of all perfused tumor pixels per mouse.

Discussion and Conclusion Multi-agent tracer-kinetic analysis demonstrated an early increase in extraction fraction of the dendrimer-based contrast agents, which was accompanied by a reduction in blood flow and increase in mean capillary transit time. Simultaneous assessment of these parameters enabled the identification of the main mechanism of vascular shut-down induced by DMXAA treatment, which is known to be via increased microvascular permeability. These preliminary results demonstrate the potential of the multi-agent tracer-kinetic modeling approach to obtain a detailed evaluation of antivascular therapies.

Acknowledgements The authors would like to thank Henk Janssen and Henk Keizer from SyMO-Chem BV (Eindhoven, The Netherlands) for synthesis of the dendrimer-based contrast agents and valuable discussions. This research was supported by the Center for Translational Molecular Medicine (VOLTA).

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