

Multi-parametric MR imaging for anti-angiogenic tumor treatment monitoring – a preclinical study

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Introduction

Early monitoring of anti-angiogenic tumor treatment and the analysis of its microvasculature is of high interest in oncology research. From previous studies, it becomes clear that classical endpoints in oncology -such as tumor size regression- will widely not suffice to monitor anti-angiogenic treatment response. Therefore, sensitive tools for quantification of changes in tumor physiology (e.g. perfusion, oxygenation, metabolism), cellularity and apoptosis are desired. Dynamic contrast enhanced (DCE-) MRI, using clinically approved low-molecular Gd-chelates, is widely established, but suffers from permeability and arterial input artifacts. USPIO enhanced “steady state” MRI and diffusion weighed imaging (DWI) are new promising methods. “Steady-state” MRI, using long-circulating USPIOs allows for sensitive $\Delta R2$ and $\Delta R2^*$ relaxometry, which gives insight into physiologic parameters like the vascular volume fraction (VVF) [1] and the mean vessel size of a tumor (VS) [2,3]. Apparent diffusion coefficient (ADC) derived from diffusion weighted imaging (DWI) allows for the non-invasive assessment of the tissue cellularity. The purpose of our study was to evaluate the usage of multi-parametric “steady-state” MR imaging and DWI for the early assessment of anti-angiogenic treatment effects using SU11248 (Pfizer, Germany) in a preclinical study.

Material and Methods

MDA-MB 435 bearing nude mice were treated over one week (day 0 and 3) with the anti-angiogenic, multi-targeted tyrosine kinase inhibitor SU11248 (Pfizer; 60mg/kg, n=5) or saline (NaCl 0.9%, n=5) as control respectively. Multi-parametric MR imaging was performed before (baseline) and after therapy (follow-up) on day 7. Imaging was done on a clinical 3T MR-Scanner (Intera, Philips). The ADC map was generated from the following DWI data: 2 slices à 2mm, $\Delta x=0.7$ mm, TR=2s, b=300, 600, 1000mm²s⁻¹. A multi-spin-echo sequence for $\Delta R2$ (28 echoes, TE: 6.9-192.1ms, TR.:2634ms) and a multi-gradienten-echo sequence (13 echoes, TE: 3.2-51.2ms, TR: 262ms) for $\Delta R2^*$ determination was applied before and after USPIO (SHU 555 C, Bayer-Schering Pharma; 80µmol/kg) injection. A vessel size index map was calculated voxel-by-voxel using the ADC map and the $\Delta R2$ and $\Delta R2^*$ maps[2,3]. From these maps, mean values over the whole tumor region were obtained for $\Delta R2^*$, the mean vessel size, and the ADC value. Furthermore, the vascular volume fraction (VVF), as a known surrogate marker of the micro vessel density (MVD), was calculated by $VVF = \Delta R2^*_{tumor} / \Delta R2^*_{muscle} \times 1.89\%$ [4]. MR results were compared with the change of the tumor size and morphometric analysis of the tumor tissue on CD31 stained tumor sections measuring the MVD and the vessel diameter. For statistical analysis, an unpaired t-test was performed.

Results

After anti-angiogenic SU11248 treatment, multi-parametric MRI revealed a significant reduction of $\Delta R2^*$ (baseline: 18.75 ± 1.51 vs follow-up: 10.41 ± 0.21), the VVF (baseline: 4.00 ± 0.52 vs follow-up: 1.67 ± 0.08) and the mean vessel size (baseline: 36.83 ± 2.90 vs follow-up: 21.47 ± 0.12) compared to control (see Fig.:1A-C). $\Delta R2^*$ - and vessel size maps clearly visualized a reduction of the tumor blood volume (VVF) in the tumor center by widely unchanged “hot spots” of mature vessel at the tumor rim(see Fig.:3). ADC- maps showed a clear water diffusion increase in terms of a reduced tumor tissue cellularity (see Fig.:1D). In line with the $\Delta R2^*$ and VVF, the histological counted MVD decreased significantly after treatment compared to the control group (SU11248: 27.25 ± 2.52 vs. control: 43.20 ± 0.09 ; Fig.:2D). Immunohistologically measured mean vessel diameters confirmed the MR vessel size distribution (SU11248: 16.30 ± 1.09 vs. control: 22.75 ± 1.00 ; Fig.:2C), although the absolute vessel diameters were overestimated with MRI. Moreover, SU11248 therapy over one week resulted in a tumor size regression of about -35%, whereas the untreated control group showed a tumor size progression of about 77% (see Fig.:2A+B).

Conclusion

Multi-parametric MR imaging allows anti-angiogenic tumor treatment monitoring by non-invasive visualization of tumor microvascular and cellularity changes. This could support further understanding of anti-angiogenic action in pre-clinical studies and early treatment monitoring in patients.

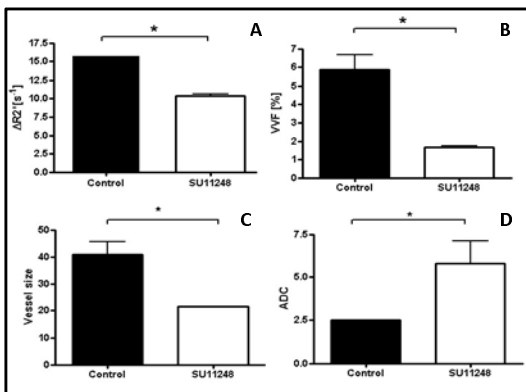


Fig.:1 After 7 days (treatment twice weekly), $\Delta R2^*$, the VVF and the mean vessel size decreased significantly, clearly reflecting the reduction in tumor perfusion in the treated animals compared with control animals (A-C). The ADC-value increased according to a reduced tumor tissue cellularity compared to the controls (D).

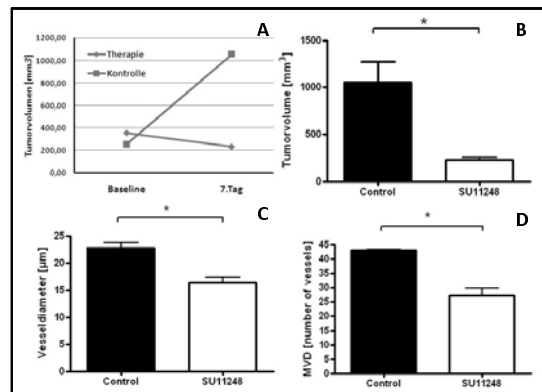


Fig.2: On day 7, the tumor size of the treated animals significantly decreased, while it increased in the control group (A+B). In line with the MR estimate of the mean vessel size, the immunohistologically vessel diameter and the MVD decreased significantly (C*D).

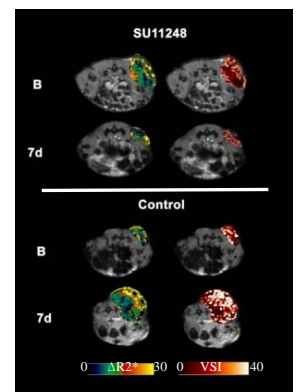


Fig.:3: Representative parametric $\Delta R2^*$ -maps (left) and VSI-maps (right) for the SU11248 group (upper box) and control group (lower box) at baseline (upper row) and day 7 (lower row).

References: [1]Persigehl T Radiology 244(2):449-56 2007, [2] Tropès I, MRM 45, pp 397-408, 2001, [3] Kiesele VG et al, MRM 53, pp 553-563, 2005, [4] Bremer C, et al, Radiology 226, pp 214-220, 2003