Value of dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted MRI (DW-MRI) for the monitoring of the effect of a vascular targeting agent on rodent tumors.

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Introduction:

Vascular targeting agents such as the combretastatins are drugs that selectively lead to an acute vascular shutdown of tumor vessels without affecting normal organs [1,2]. The purpose of our study was to compare dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted MRI (DW-MRI) for the noninvasive evaluation of early and late effects of a vascular targeting agent on rhabdomyosarcomas in rats.

Material and Methods:

Nine rats with rhabdomyosarcomas in both flanks (n=18) underwent conventional MRI before (T1-w SE, T2-w TSE) and after (fat saturated T1-w SE) contrast medium administration as well as DCE-MRI (dynamic 3D gradient-echo sequence with fat saturation, VIBE) and echo-planar DW-MRI in a 1.5 T SONATA MR unit (Siemens, Erlangen, Germany). Imaging was performed using a 4-channel wrist coil; a GRAPPA-factor of 2 was applied for all sequences. This protocol was performed before, early (1 and 6 hours) as well as later (2 and 9 days) after intraperitoneal injection of Combretastatin A-4 phosphate (CA-4-P, OXiGENE, Watertown, MA; 25mg/kg body weight). Histopathologic correlation was obtained by sacrificing one rat at each time point. Conventional MRI was used for morphologic evaluation of perfused and nonperfused areas. DW-MRI was analyzed by drawing regions of interest (ROIs) on the calculated apparent diffusion coefficient (ADC) maps at each time point (ADC_{avg}). To differentiate the influence of perfusion and diffusion ADC was separately calculated for low (b=0, 50, 100 s/mm^2; ADC_{low}) and high b values (b=500, 750, 1000 s/mm^2; ADC_{high}). DCE-MRI was quantified by calculating the rate constant k to demonstrate changes in permeability of the tumor vasculature; the initial slope was calculated in order to evaluate the time course of enhancement.

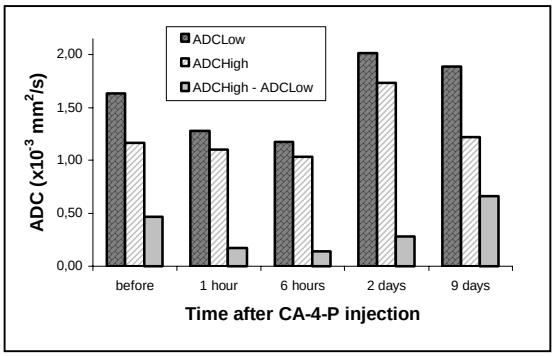

Figure 1: Time course of ADC_{low} (b=0,50,100 s/mm^2), ADC_{high} (b=500, 750, 1000 s/mm^2) and their difference before and after injection of CA-4-P.

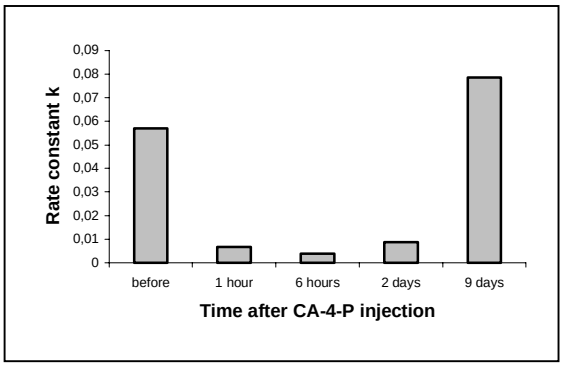

Figure 2: Time course of the rate constant k, calculated from the DCE-MR images before and after intraperitoneal injection of CA-4-P.

Results:

Early after CA-4-P administration contrast-enhanced T1-w SE images showed a decrease of solid enhancing tumor tissue with increase of nonperfused areas. The corresponding ADC_{avg} as well as the ADC_{low} decreased significantly ($p<0.001$) (Fig. 1). However, the ADC_{high} remained mainly unchanged (Fig. 1) indicating still viable tumor tissue, confirmed by histology. Both k (Fig. 2) and the initial slope decreased significantly at the same time points which correlated to a decrease in ADC_{low}. At two days the necrotic tumor fraction strongly increased, whereas at nine days regrowth of the rim was seen on the contrast-enhanced MRI images (confirmed by histology). This was reflected by a decrease in ADC_{avg} at two days and an increase at nine days after CA-4-P injection. In parallel, k (Fig. 2) and the initial slope increased from two to nine days.

Discussion:

DW-MRI and DCE-MRI provide similar information on the effect of vascular targeting compounds. The use of low and high b-values for the calculation of the ADC allows to separate the influence of perfusion and diffusion. The ADC_{high} approximates true diffusion, whereas the ADC_{low} reflects both diffusion and perfusion. Therefore, the difference between ADC_{low} and ADC_{high} approximates perfusion. This perfusion is paralleled with the k value provided by DCE-MRI (Figs. 1 and 2). The ADC_{high} gives information about the integrity of the underlying tumor cells and can therefore be used to differentiate viable and necrotic tissue.

References:

1) Tozer G. M. et al. Int J Exp Pathol **83:**21 (2002).
2) Landuyt W. et al. Eur J Cancer **36:**1833 (2000).