Effects of the anti-vascular agent, combretastatin-A4-phosphate, on 1H MRI relaxation times in colon tumour xenografts

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Synopsis: The effects of combretastatin-A4-phosphate (CA4P) on 1H relaxation times at 4.7T were studied in SW1222 colon carcinoma xenografts in nude mice. CA4P (30, 100 or 200mg/kg) or saline were administered i.p. either 4 or 24 hours before MR examination. Significant increases in T1, T2 and T2* were observed 24 hours after 100 and 200mg/kg CA4P. These were consistent with an increase in necrosis and reduction in vascular volume but not with anticipated haemorrhage and reduced oxygenation.

Introduction: Combretastatin-A4-phosphate (CA4P) is a tubulin-binding agent which has been shown to selectively damage tumour vasculature [1]. MR techniques, especially DCE-MRI and 31P MRS have previously been used to monitor the anti-vascular effects of CA4P in animal tumour models [2,3]. The aim of this study was to use several MR endpoints to investigate the dose-response relationship of CA4P in the SW1222 colon carcinoma xenograft in nude mice. In addition to effects on blood flow and on metabolism, we hypothesise that induction of haemorrhage, oedema, hypoxia and necrosis will be reflected in changes in tumour 1H relaxation times. The effects of CA4P on tumour relaxation times (before injection of contrast agent) are reported here.

Methods: SW1222 tumour cells were implanted subcutaneously onto the rear dorsum of female MF1 nude mice. Tumours were selected when approximately 6-9mm in gross maximum diameter. CA4P (30,100 or 200 mg/kg) or saline were given i.p. either 4 or 24 hours before MR examination. Mice were sedated (fentanyl citrate 0.0945mg/kg and fluanisone 3mg/kg) and restrained in a 6cm quadrature birdcage coil within the horizontal bore 4.7 T magnet of a Varian MR system. Mouse body temperature was monitored continuously with a rectal probe and maintained with a warm air blower. A single slice (2mm thick, FOV 40x45mm) was located through the centre of the tumour and the following MRI data obtained: spin-echo with TR=1000ms TE=11,60ms; multi-gradient-echo with TR=234ms, TE=4,8,12,16,20,24,28,32ms α=45°; inversion recovery T1 with TR=2420ms, TI=100,400,800,1600,2400ms TE=10ms. T1 and T2* maps were calculated from the corresponding data sets. T2 maps were estimated from the two spin-echo images. A tumour ROI was defined from the TR=1000 TE=60 spin-echo image. Five to seven animals were used for each treatment group. Statistical comparisons involved unpaired t-tests.

Results: Baseline relaxation times (median +/- sd) were obtained from saline-treated animals: T1 = 1.82s +/- 0.19s; T2 = 38.3ms +/- 2.2ms; T2* = 9.5ms +/- 2.8ms. CA4P 30mg/kg had no significant effect on these parameters. There were also no significant changes at 4 hours after all doses of CA4P. However, significant increases in all parameters were observed 24 hours after injection of CA4P at 100mg/kg and 200mg/kg, as summarised in Figure 1.

Figure 1: Tumour 1H relaxation times 24 hours after CA4P or saline: (a) T1; (b) T2; (c) T2*.

Discussion: The effects of anti-vascular agents on tumour relaxation times are not entirely predictable. A decrease in water 1H relaxation times, especially T2*, might be expected as these drugs can cause haemorrhage and haemorrhagic necrosis [1]. However, CA4P results in increased vascular permeability to macromolecules [4] which may lead to oedema. The subsequent increase in extracellular space could increase water 1H relaxation times. This effect may be augmented if tumour deoxyhaemoglobin levels fall due to a reduction in vascular volume [1]. In the present study, high doses of CA4P (100-200mg/kg) caused an increase in T1, T2 and T2* relaxation times at 24 hours. The T2* changes were especially marked and had the clearest dose-response (about 2-fold for 100mg/kg and 3-fold for 200mg/kg). The results indicate that haemorrhagic events, if occurring, have relatively little influence on tumour 1H water relaxation at 4 and 24 hours in this tumour model. The dramatic increase in T2* is consistent with a reduction in vascular volume but is not consistent with the anticipated reduction in tumour oxygenation [5].

References:
[5]. Seddon BM et al., Clin Cancer Res. 2002 8: 2323-35.