Measuring ADC reductions as an early response to chemotherapeutic treatment

L. J. Bains[1], J. H. Baker[2], A. I. Minchinton[2], and S. A. Reinsberg[1]

[1]Physics and Astronomy, University of British Columbia, Vancouver, British Columbia, Canada, [2]Medical Biophysics, British Columbia Cancer Research Centre, Vancouver, British Columbia, Canada

Introduction

Tirapazamine is a prodrug which is activated under hypoxic conditions. Minchinton *et al.* have shown that tirapazamine induces vascular shutdown and central necrosis [1]. To investigate this effect, the apparent diffusion coefficient (ADC) was mapped before and after treatment and aligned with BrdU/haematoxylin images of necrosis. Tirapazamine caused a decrease in mean ADC within 24 hours after treatment, while also causing an increase in the fraction of necrotic tissue per tumour. Tumours with higher pre-treatment ADC showed a diminished response, indicating that ADC may be a predictor of response to tirapazamine.

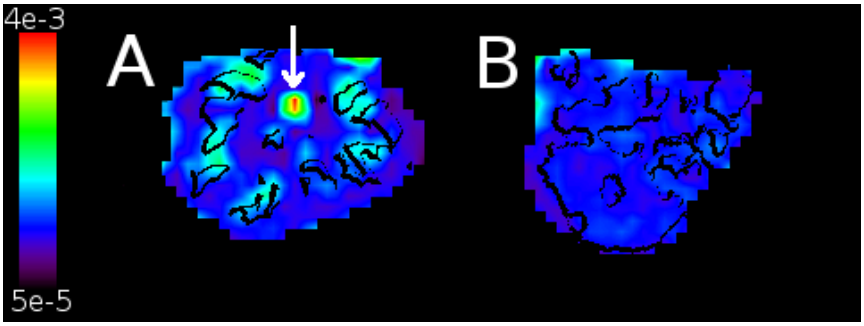

Figure 1: ADC maps of control (A) and treated (B) tumours, with areas of histological necrosis outlined in black. High ADC is seen in necrotic regions of controls but not in treated tumours. Note the high-ADC fiducial marker visible in the control tumour (white arrow).

Materials and Methods

Mice: Fourteen SCID mice with subcutaneous HCT-116 (human colorectal cancer) xenografts and implanted fiducial markers received one MRI scan immediately prior to tirapazamine treatment and a second scan at 24 hours after tirapazamine/vehicle treatment. Tumour excision was performed after the second scan.

MRI: Imaging was performed on a 7 T Bruker Biospec 70/30 using a custom-built 4 turn distributed-capacitor solenoid. A two-TR FLASH protocol (TR=226 ms and 113 ms, TE=6ms) was used for the calculation of concentration of contrast agent with a spatial resolution of 0.3x0.3x1.0 mm and a time resolution of 14.5s. 30 minutes of the TR=113 FLASH were acquired following a 10µl/g bolus of Gd-DTPA (0.3 mmol/kg). A diffusion-weighted EPI with the same slice geometry as the FLASH scans and TR/TE=3000/26 ms, b=0, 500 s/mm^2, BW=200 kHz was used to calculate ADC. A standard Kety model was used to find the fraction of extravascular extracellular space (v_e).

Immunohistochemistry: A robotic microscope with x-y-z stage was used to acquire whole-section haematoxylin/BrdU images from tissue slices corresponding to MRI imaging slices. An experienced observer used haematoxylin and BrdU images to outline areas of histological necrosis.

Results and Discussion

ADCs are typically expected to be higher in necrotic areas than in healthy tissues [3]. This effect was seen in controls, and in all tumours prior to treatment: mean ADC in areas of histologically defined necrosis was higher than in areas which were non-necrotic. However, treatment with tirapazamine triggered both a significant decrease in mean whole tumour ADC (figure 2) and a homogenization of ADCs throughout the tumour (post-treatment ADC values in necrotic and non-necrotic regions were not significantly different). While a decrease in ADC after treatment may be counter intuitive, decreases in ADC triggered by vascular targeting agents have been measured previously by Mardor *et al.* [4]. In addition to decreased ADCs, treated tumours showed a significantly greater percentage of histologically defined necrosis than controls, and a significant decrease in the v_e of non-necrotic tissues. As observed by Leach *et al.*, v_e may either increase or decrease in response to treatment and is a somewhat ambiguous measure of treatment response [2].

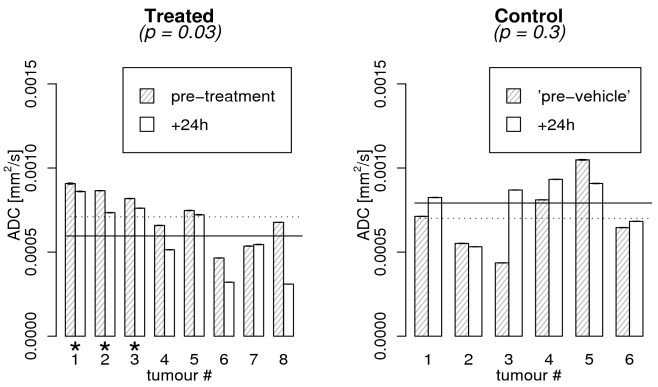

Figure 2: Mean whole-tumour ADC before (hashed) and after (white) treatment. A significant difference was observed between the population means before (dashed) and after (solid) treatment, while controls showed no significant change. Partial responders are starred.

Using immunohistochemistry, an experienced observer (JHB) identified three tumours as showing a diminished response to tirapazamine. These 'partially responding' tumours were found to have a significantly higher pre-treatment ADC than the other treated tumours.

Conclusions

Tirapazamine treatment caused a significant decrease in whole tumour ADC, increase in necrosis, and increase in v_e for non-necrotic tissues. Elevated ADC was identified as a potential predictor of decreased tumour response to tirapazamine.

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[3] D. Hamstra, et al., JClin Oncol 25 (2007) 4104– 4109.
[4] Y. Mardor, et al., Cancer Res 61 (2001) 4971–3.