DCE-MRI analysis of radiotherapy and Combretastatin-A4-Phosphate (CA4P) effects on the cancerous prostate gland

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Background

Preclinical studies[1] have shown a potential therapeutic benefit with the addition of vascular disruptive strategies to radiotherapy, including the tubulin-binding agent Combretastatin-A4-Phosphate (CA4P). CA4P produces marked vascular shutdown in tumours, which in turn leads to central necrosis. Radiotherapy is most effective in regions where there is sufficient blood supply and minimal hypoxia. By combining these two therapeutic modalities, there is the potential to target different parts of the tumour and hopefully produce greater cell kill. The aim of this study was to document changes in prostate gland vascularity by dynamic MRI during and after radical radiotherapy with a single dose (50mg/m^2) of combretastatin-A4-phosphate (Oxigene Inc., USA) in a Phase Ib toxicity-determining study.

Methods

Six patients (mean age 68y) undergoing radical radiotherapy following neoadjuvant hormonal therapy for prostate cancer (Gleason >6, PSA >20ng/ml or T3/4), were evaluated by multislice dynamic contrast-enhanced MRI on nine occasions: two baselines (1&2), following 5 fractions RT (3), 4h (4) & 72h following CA4P (5), after 12-15 fractions RT (6), end of RT + 1 month (7), 3 months (8) and 6 months (9). Patients were studied using a 1.5T Siemens Symphony scanner. T_1 weighted DCE-MRI studies were obtained using methods previously described[2]. Briefly, spoiled GRE [FLASH] sequences (TE 4.7ms, TR 11ms, α=35^o, 3 slices) were acquired before and after the bolus administration of 0.1 mmol/kg bw of Gd-DTPA with 40 time points over 8 min, through the prostate gland. Transfer constant (K^{trans}) and extracellular leakage space (v_e) were calculated pixel-by-pixel for the scanned prostate volume using Tofts' methods and MRIW software[3,4]. Changes in median values of parameters were analysed with reference to the technique's repeatability and with paired *t*-tests.

Results

Figures 1 and 2 show the individual and mean K^{trans} changes over the study period. Significant group increases in K^{trans} (p=0.02) were seen following 5 fractions of RT (with 5/6 patients showing individual increases). Mean K^{trans} values decreased significantly after the last radiotherapy fraction (between time points 6 and 7: p=0.04). Six months after therapy, K^{trans} values remained elevated compared with baseline (p=0.04). Significant group increases in v_e (p=0.0012) were seen following 5 fractions of RT (no individuals showed a significant increase). The trend of increasing leakage space was maintained, apart from a transient decrease 4h following CA4P administration (time point 4). At the end of the study period, v_e was still significantly elevated compared with baseline (p=0.007).

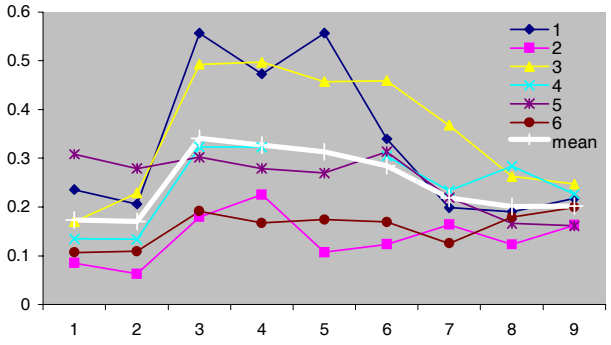

Figure 1: Median ROI values for each patient studied at the specified time points. The thick white line is used to represent the mean values for the study group.

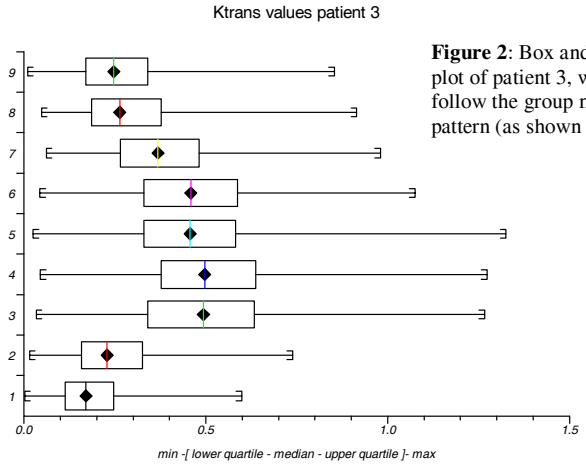

Figure 2: Box and whisker plot of patient 3, whose data follow the group mean pattern (as shown in fig. 1)

Discussion and Conclusion

Quantifiable acute changes in the MR vascular kinetic parameters are noted following radiotherapy demonstrating an early increase in K^{trans}. The lack of significant decreases in K^{trans} following CA4P is counter to previously published data on CA4P used alone[5]. Increases in leakage space may indicate decreasing cellularity, which is in keeping with the expected effects of radiation treatment. In conclusion, radiotherapy appears to modulated the expected vascular shutdown of CA4P, emphasising the need for mechanistic combination therapy studies to understand therapy effects.

References

[1]Chaplin DJ, *Anticancer Res*. 1999; **19**: 189-195.
[2]Lankester KJ, *Br J Cancer*. 2005 Oct 31;**93(9):**979-85.
[3]Tofts, PS and Kermode, AG. JMRI 1997; 7:91
[4]d'Arcy JA, RadioGraphics 2006; 26:621
[5]Galbraith SM, Maxwell, RJ, et al. *J Clin Oncol*. 2003; **21**(15): 2831-42