DCE-MRI for assessment of effects of anti-angiogenic therapy: Comparison of the transfer constant (Ktrans) to blood permeability derived by a distributed parameter model.

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Introduction

Dynamic contrast enhanced MRI (DCE-MRI) with tracer kinetic modeling has been proposed as a biomarker of angiogenesis imaging. Generalized kinetic (GK) model (1) and uptake integral approach (2) are commonly used DCE-MRI models whose representative parameters are Ktrans (1) and initial area under the signal-time curve (IAUC) (2), respectively. The distributed parameter (DP) model (3) is a DCE-MRI model that enables derivation of blood flow and capillary permeability-surface area product (PS) independently. We aim to study the DP model as an alternative method of angiogenesis assessment and correlate the above parameters to drug exposure and patient outcome in a Phase I anti-angiogenic trial.

Materials and methods

Patient

Twenty evaluable patients from an on-going phase I trial (ABT 869) with 3 dose escalations formed the study population. Pharmacokinetic study was performed on Day I. Area under the concentration time curve extrapolated to infinity (AUC_{inf}) was used as an indicator of drug exposure. Patients demonstrating progressive disease in first 2 evaluation scans (cycle 2 or 4) based on RECIST criteria were considered progressors and all other patients non-progressors.

DCE-MRI

MRI was performed on a 1.5 Tesla scanner (Avanto, Siemens, Erlangen) using integrated surface coils (TIM, Siemens, Erlangen). A three-dimensional, fast low-angle shot (3D FLASH) sequence was used to acquire sequential images with the following parameters: repetition time TR=3.15 ms, echo time TE=1 ms, field of view (FOV) 40cm×40cm, 256×256 matrix, 10 slices with slice thickness 8mm, and temporal resolution 4 sec. To estimate native (pre-contrast) tissue T_1 values using the dual-flip angle method, 5 sets of pre-contrast images were acquired with the above parameters for each of two flip angles, a = 6° and 10°. This is followed by a dynamic sequence which includes 90 consecutive sets of images acquired with the above parameters and a flip angle a=10°. Intravenous Gd-DTPA (Magnevist®, Bayer Schering Pharma, Berlin, Germany) at 0.2mmol/kg was injected after the 10th set of dynamic images at 3 ml/sec followed by a 20 ml saline flush at the same rate..

Data processing & statistical analysis

Post-processing was performed off-line on a Pentium IV personal computer with Matlab™ (MathWorks, Natick, MA). Region-of-interests (ROIs) consisting of the tumor were manually identified. ROI over aorta was used as arterial input function. Percentage change in DP_PS, Ktrans, and IAUC from BL in D3 and D15 were compared with the patient response. Receiver operating characteristic (ROC) curve analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, IL). Correlation with AUC_{inf} was done using Medcalc (Medcalc Software, Mariakerke, Belgium).

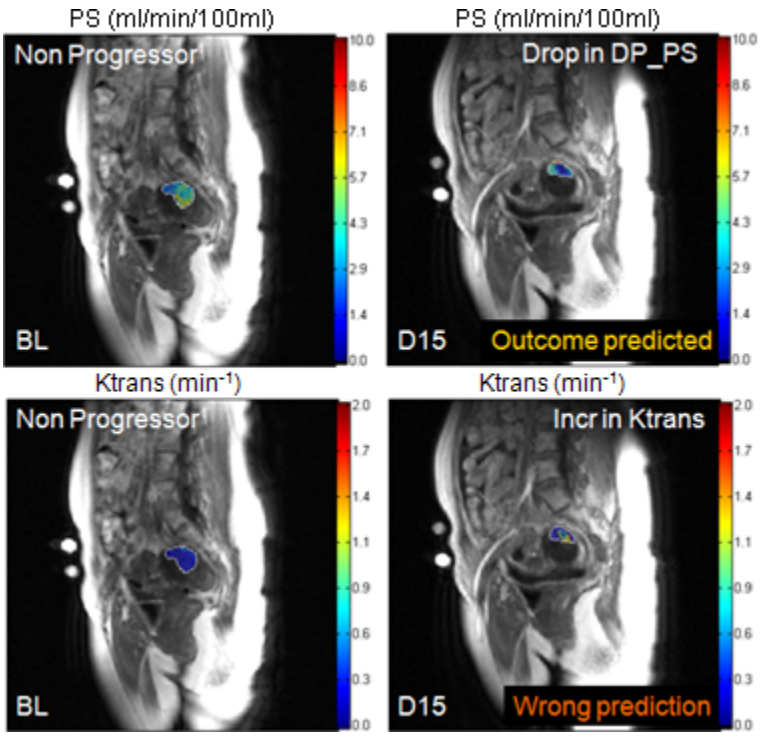
Results

Correlation with drug exposure (AUC_{inf})

There is good correlation between DP_PS and AUC_{inf} (Spearman's coefficient -0.557, p = 0.015). Although stronger correlation is found with IAUC (Spearman's coefficient -0.683, p = 0.003), the difference is not significant (p = 0.548). There is no correlation for Ktrans (Spearman's coefficient -0.128, p = 0.577)

ROC analysis for predicting progressor & non-progressor

ROC area for DP_PS is higher than that of Ktrans (0.868 versus 0.429, p < 0.001). IAUC showed a lower area compared to DP_PS (0.692 versus 0.868) but the difference is not significant (p = 0.156). Using a 27.4% drop from baseline to predict non-progressors, the sensitivity of DP_PS is 69.23% and the specificity is 100% whereas sensitivity of Ktrans is 38.5%, and specificity 42.86%. In 8 out of 20 cases (40%), DP_PS correctly predicted the eventual outcome whereas Ktrans gave the wrong prediction.



Example where PS predicted the outcome correctly and Ktrans predicted wrongly

Conclusion

Permeability-surface area product (PS) derived from distributed parameter model shows better correlation with drug exposure and may predict patient outcome better than Ktrans. It also performs reasonably well compared to IAUC, a parameter with heuristic approach.

References

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