Comparison of tracer kinetic models with DCE-MRI to evaluate a phase 1 anti-angiogenic trial

C. H. Thng[1], T. S. Koh[2], S. Hartono[1], B. C. Tai[3], P. S. Lee[1], H. Rumpel[4], A. B. Ong[5], N. Sukri[5], C-I. Wong[5], R. Soo[5], A. S. Low[4], R. Humerickhouse[6], and B. C. Goh[5]

[1]National Cancer Centre Singapore, Singapore, Singapore, Singapore, [2]Nanyang Technological University, Singapore, Singapore, Singapore, [3]National University of Singapore, Singapore, [4]Singapore General Hospital, Singapore, [5]National University Hospital, Singapore, [6]Abbott Laboratories, United States

Introduction

Dynamic contrast enhanced MRI (DCE-MRI) with tracer kinetic modeling has been proposed as a biomarker of angiogenesis imaging. Three tracer kinetic models were studied as methods of angiogenesis assessment: conventional compartmental (CC) model developed by Brix et al. (1), adiabatic approach to tissue homogeneity (ATH) model developed by St. Lawrence and Lee (2), and distributed parameter (DP) model developed by Koh et al. (3) All models enable derivation of tissue microcirculatory parameters such as blood flow and capillary permeability-surface area product (PS). We aim to examine the association between the above parameters with drug exposure and patient outcome in a Phase I anti-angiogenic trial.

Materials and methods

Patient

Twenty-eight evaluable patients from a completed phase I trial (ABT-869) with 3 dose escalations formed the study population. The 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 18°. This is followed by a dynamic sequence which includes 90 consecutive sets of images acquired with the above parameters and a flip angle a=18°. 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 PS derived from each model (DP_PS, ATH_PS, and CC_PS) from baseline in Days 3 and 15 were compared with the patient response. Receiver operating characteristic (ROC) curve analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, IL). Correlation with C_{max} and AUC_{inf} was done using Medcalc (Medcalc Software, Mariakerke, Belgium).

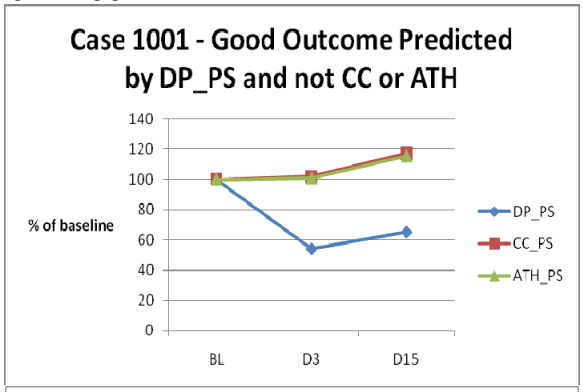
Results

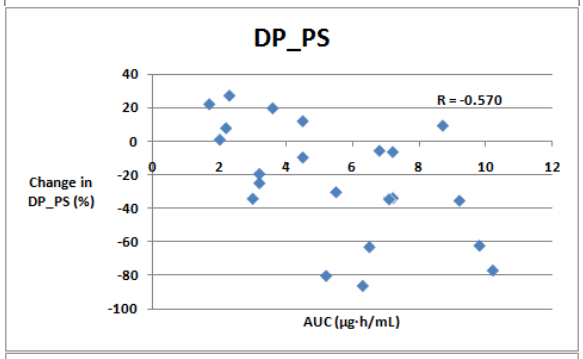
Correlation with drug exposure (AUC_{inf})

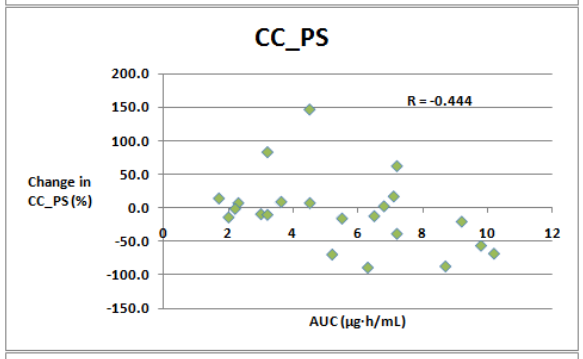
Significant inverse correlation was observed between ABT-869 AUC_{inf} and DP_PS as well as CC_PS on day 3 (r = -0.564, p = 0.015; r = -0.716, p < 0.001) and day 15 (r = -0.570, p=0.006; r = -0.444, p = 0.038). There is no correlation between ATH_PS with AUC_{inf} both in day 3 and day 15. The scatter diagram for each model PS in day 15 as plotted against AUC_{inf} is shown in Figure 1.

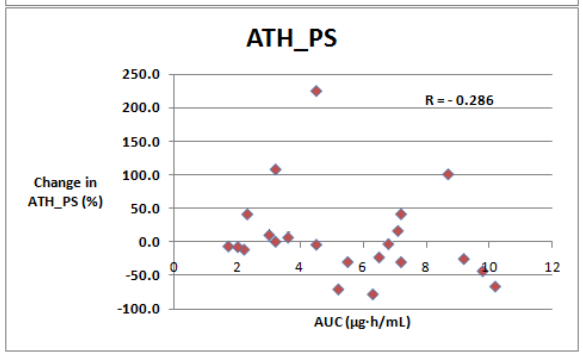
ROC analysis for predicting progression and at Day 15

Of the three models, only DP_PS shows significant area under the ROC curve (Area = 0.779, 95% CI 0.549 to 0.906). Using a 25.1% drop from baseline to predict non-progressors, the sensitivity of DP_PS is 64.7% and the specificity is 87.5%.









Conclusion

Permeability-surface area product (PS) derived from the distributed parameter model shows better correlation with drug exposure and may predict patient outcome better than PS derived from the conventional compartmental model and the adiabatic tissue homogeneity model.

References

1. Brix G, et al. Radiology 1999; 210:269-76.
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3. Koh TS, et al. IEEE Trans Biomed Eng 2003;50:159-167.