Dynamic contrast enhanced MRI (DCE-MRI) for predicting clinical response to bevacizumab and chemotherapy in previously untreated inflammatory breast cancer: a comparison of analytic methods

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Introduction: Solid tumors require new blood vessels in order to grow, a process known as angiogenesis.[1] Antiangiogenic therapy targeted to inhibit VEGF, such as bevacizumab (BV), is an attractive approach to the treatment of cancer. Diagnostic tools, such as dynamic contrast enhanced MRI (DCE-MRI), that provide early indications of the success or failure of treatment may be important for directing appropriate therapy.[2] The objective of this study was to compare three models of DCE-MRI analysis (Brix, Heuristic, and General Kinetic Model) and determine which parameter or combination of parameters best predicted clinical response to this therapy.

Methods: Twenty one patients with previously untreated inflammatory breast cancer were treated with BV alone for cycle 1 (15 mg/kg on day 1) followed by six cycles of BV (15mg/kg) with doxorubicin (50mg/m^2) and docetaxel (75 mg/m^2) every 3 weeks and G-CSF for cycles 2-7. DCE-MRI images were obtained at baseline, after cycle 1, 4, and 7. Measurable disease and clinical response were assessed by imaging using the Response Criteria in Solid Tumors (RECIST) criteria.[3] MRI of the breast was performed on 1.5 Tesla MRI system (General Electric Medical Systems, Waukesha WI) obtaining bilateral breast images using a 3D SPGRE sequence with a TR 7.8/TE 4.2/FA in a 512 x 512 matrix size and 5 mm slice thickness. We acquired 20 dynamic data sets after a total of 0.1mmol/Kg (typically between 15 and 20cc) of gadolinium Magnevist injected at a rate of 0.3cc/sec for a temporal resolution of 29.9 seconds. Regions of Interest (ROIs) were drawn around the most enhanced area in the tumor excluding necrotic areas. We analyzed the data using three methods: 1) Heuristic model: a direct measurement of wash-in and wash-out slopes and the area under the curve (AUC) for the first 90 seconds after injection; 2) Brix model: derived parameters, Amplitude and k_{ep}; 3) General Kinetic Model (GKM): derived parameters, k_{trans}, k_{ep}, and v_e. All models were implemented in IDL-based computer programs, Brix and Heuristic model courtesy of Dr Michael Knopp and GKM courtesy of GE Research software "Cinetool."[4] In an exploratory fashion, absolute values and relative changes of all parameters at baseline, cycle 1, cycle 4, and cycle 7 were compared between responders and non-responders using an exact Wilcoxon rank sum test. P<0.01 is required for statistical significance because of multiple comparisons.

Results: Of the 20 patients assessed (1 patient was unable to undergo MRI), 13 were clinical responders with a partial response (PR) and 7 were non-responders with stable or progressive disease (SD/PD). Figure 1 demonstrates a representative example of DCE-MRI images taken from one responding patient from baseline to cycle 7 of treatment. Statistical analyses comparing all baseline parameters showed trends toward differences between responders and non-responders for slope wash-in (p=0.036) and slope wash-out (p=0.016) from the Heuristic model. In addition, when examining the relative differences from baseline to C1 according to response, only values for the Heuristic AUC (p=0.049) and slope wash-out (p=0.049) differed according to response. The relative differences from baseline to C4 only showed the Heuristic AUC parameter to be noteworthy (p=0.032). Figure 2 illustrates the Heuristic AUC parameter at baseline and change from baseline to C1 and C4. Although the baseline AUC does not significantly discriminate between responders and non-responders, the change from baseline to C1 and baseline to C4 may be predictive.

Discussion: We found that the slope wash-in and slope wash-out (derived using the Heuristic model) correlated best with clinical response at baseline. These results may allow us to use these parameters to appropriately select patients for this treatment regimen. Similarly data for the change from baseline to cycle 1 and baseline to cycle 4 showed that AUC (also from the Heuristic model) was best able to discriminate between responders and non-responders. Although baseline AUC was not predictive, the change in AUC from baseline to C1 and baseline to C4 may be used as a tool to evaluate clinical response early in therapy to allow for change in treatment if needed. The literature on DCE-MRI predominantly describes two types of models used to evaluate the pathophysiology: 1) Pharmacokinetic (PK) models such as Brix, Tofts, and GKM (Kety) and 2) Descriptive models such as the Heuristic model that use parameters such as wash-in and wash-out slopes and AUC. The advantage of PK models is that their parameters have a direct physiologic correlate, however, the disadvantage is that assumptions implicit in models may be incorrect. Consequently, an advantage of the Descriptive models is that in their simplicity they may be more statistically robust. Although we found that parameters such as slope wash-in, slope wash-out and AUC were best for predicting clinical response, future work will be needed to incorporate the advantages of both types of analyses.

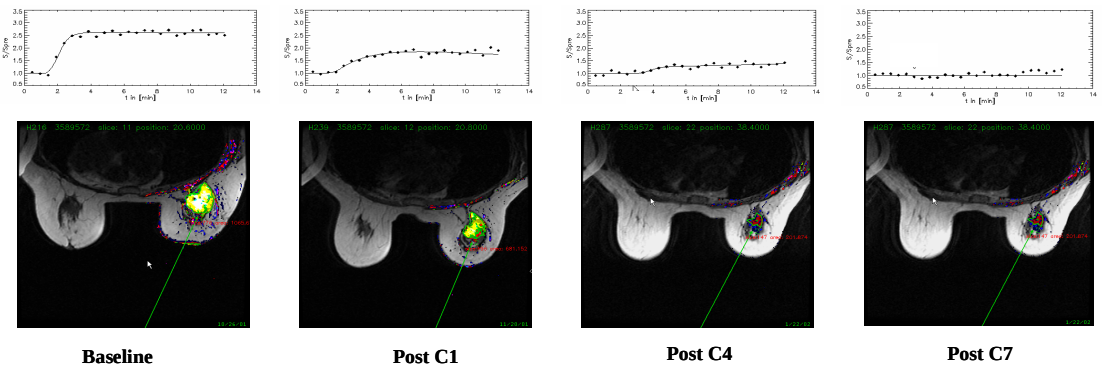

Figure 1. Change in contrast enhancement and time intensity curves from baseline to post C7 for a responding patient.

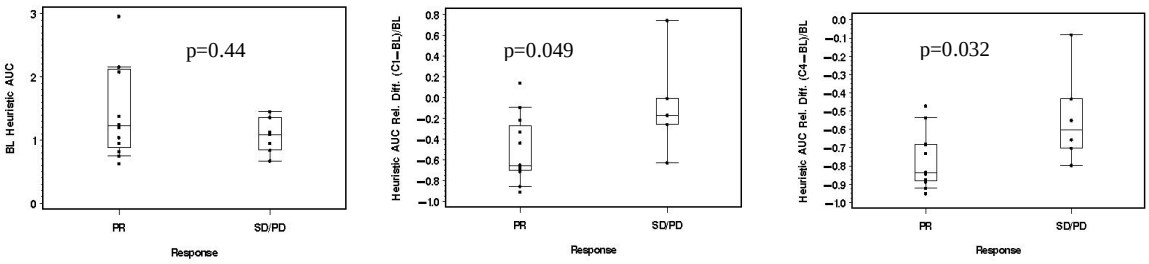

Figure 2. Heuristic AUC data comparing responders (PR) vs. non-responders (SD/PD) for baseline (BL), change from BL to C1, and change from BL to C4, respectively.

References: [1] Folkman J. N Engl J Med 1971; 285: 1182-1186.; [2] Knopp MV et al. J Magn Reson Imaging 1999; 10:903-907.; [3] Therasse P et al. J Natl Cancer Inst 2000; 92(3):205-16.; [4] Tofts PS et al. J Magn Reson Imaging. 1999 Sep;10(3):223-32.