

## Bone Marrow DCE-MRI Prediction of Acute Leukemia Response to Therapy

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**Target Audience:** Hematologic oncologist, Radiologist, MRI scientist

**Purpose:** Relatively few prognostic biomarkers have been identified for acute myelogenous leukemia (AML) and the results of these laboratory studies are typically not available prior to therapy initiation. Thus, there is a pressing need to discover rapidly evaluable biomarkers associated with the most important therapeutic endpoint in AML, a complete remission (CR). Pre-therapy identification of patients who are unlikely to respond to conventional chemotherapy would permit swift introduction of personalized therapeutic approaches for this high risk population, preventing these patients from exposure to toxic and ineffective therapies.

Increased angiogenic activities have been observed in the bone marrow (BM) of AML patients (1), and correlations between high expression levels of some angiogenic cytokines and poor prognosis have been reported (2). By measuring tissue microvascular properties, dynamic contrast-enhanced (DCE) MRI is a powerful, minimally invasive imaging modality that has been widely used in research settings and early phase clinical trials to assess solid tumor response to therapy. A recent vertebral BM DCE-MRI study (3) reported that the pre-therapy Peak measurement (maximum percent signal intensity change) was predictive of AML patient overall survival, demonstrating the utility of DCE-MRI for non-solid tumor studies. However, the Peak metric is a semiquantitative measure and its value is highly dependent on DCE-MRI data acquisition details and parameters, and thus not an imaging biomarker that can be reproduced and standardized without difficulty across institutions. Here we present our preliminary results of pre-therapy quantitative BM DCE-MRI for the purpose of predicting CR following standard-of-care treatment of AML patients.

**Methods:** Thirteen newly diagnosed AML patients (9 males and 4 females; age: 34-68 years) consented to a research DCE-MRI study before undergoing standard induction chemotherapy. All the MRI exams were performed with a 3T Siemens Tim Trio system using the body coil and the spine matrix phased-array coil as the transmitter and receiver, respectively. Following pilot and anatomic MRI, a 3D RF-spoiled gradient-echo sequence was used to acquire coronal DCE-MRI data with  $10^0$  flip angle, TE/TR = 1.4/6.0 ms, 34-40 cm FOV, and 288x288 matrix size. Each DCE image volume set included 22 slices with 5 mm slice thickness and zero gap, covering the anterior-to-posterior spatial range of vertebral body to iliac crest where BM biopsy was performed to confirm diagnosis and remission status. A total of 60 image volumes were acquired for  $\sim$  10 min with a temporal resolution of 10 s. Gadolinium contrast agent (Prohance<sup>®</sup>) was administered (0.1 mmol/kg at 2 mL/s) through an antecubital vein following acquisitions of five baseline image volumes.

ROIs on multiple image slices were drawn encompassing vertebral bodies of L2, L3, and L4 as previously described (3), and also in the left and right iliac crest. The ROI and pixel (within the ROI) DCE-MRI signal intensity time courses were then subjected to pharmacokinetic analyses using the Tofts model (4) to extract  $K^{trans}$ ,  $v_e$ , and  $k_{ep}$  ( $= K^{trans}/v_e$ ) parameters. A population-averaged arterial input function (AIF) (5) was used for data fitting with its amplitude adjusted for each subject using the muscle tissue adjacent to iliac crest as the reference tissue region (6). Pre-contrast  $T_1$  ( $T_{10}$ ) was determined from the multi-flip angle (5°, 10°, and 20°) image data acquired just before the DCE-MRI scan. The mean pharmacokinetic parameter value of each anatomic location was calculated as the weighted (by ROI pixel number) average of the single-slice ROI parameter values. For each patient, an overall BM mean value was calculated for each parameter by averaging the mean values of the five locations (L2, L3, L4, and left and right iliac crest). Histogram analyses of the pixel parameter values were performed for all the pixels of the five locations combined together.

CR or non-CR status following therapy was determined by BM biopsy and correlated with the pre-therapy DCE-MRI metrics using the univariate logistic regression (ULR) analysis to identify imaging biomarkers for prediction of therapeutic response. The  $c$  statistics value produced by the ULR analysis is equivalent to the area under the curve (AUC) of the receiver operating characteristics (ROC) analysis.

**Results:** Among the 13 patients, 8 achieved CR following therapy while the other 5 had non-CR status. The mean  $\pm$  SD values of the BM DCE-MRI parameters are listed in **Table 1** for the two groups, showing

generally lower baseline  $K^{trans}$  and  $k_{ep}$ , and higher  $v_e$  values in the CR compared to the non-CR group. **Table 2** shows the ULR  $c$  statistics values of the ROI mean and histogram median DCE-MRI parameters for prediction of therapy response (CR vs. non-CR). The BM mean  $k_{ep}$  is an excellent predictor of CR with  $c = 0.90$ , while mean  $v_e$  is a good predictor with  $c = 0.70$ . The **Figure** displays the L3 (top) and right iliac crest (bottom)  $k_{ep}$  maps superimposed on post-contrast DCE images from a CR (left) and non-CR (right) patient. Under the same color scale, it is clearly noticeable that the pre-therapy BM  $k_{ep}$  was substantially lower in the patient eventually achieving CR compared to the one who did not.

**Discussion and Conclusion:** Consistent with the previous study (3), this study demonstrates that DCE-MRI can be a useful functional imaging modality for characterization of non-solid tumor cancer, such as leukemia. The preliminary results from 13 patients suggest that the pre-treatment contrast agent intravasation rate constant  $k_{ep}$  is an excellent predictor of CR for AML patients undergoing standard induction chemotherapy. Since  $k_{ep} = K^{trans}/v_e$ , and  $K^{trans}$  and  $v_e$  were good ( $c = 0.70$ ) and fair ( $c = 0.68$ ) predictors of CR, respectively, the high discriminative capability of the  $k_{ep}$  parameter can most likely be attributed to a combined phenomena of generally increased  $K^{trans}$  and decreased  $v_e$  in the BM of non-CR patients compared to CR patients. Continued subject enrollment is planned for this study to validate the preliminary results. Diffusion-weighted MRI measurement of cellularity could be used in future studies to verify the observed  $v_e$  difference between CR and non-CR patients. It is interesting to note that the researchers who first reported the semiquantitative Peak measures (3) showed in a recent quantitative DCE-MRI study (7) that BM  $k_{ep}$  measured in AML patients at CR was predictive of relapse-free survival.

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**References:** 1. Padro *et al.* *Blood* 2000;95:2637-44. 2. Loges *et al.* *J Clin Oncol* 2005;23:1109-17. 3. Shih *et al.* *Blood* 2009;113:3161-7. 4. Tofts *et al.* *J Magn Reson Imaging* 1999;10:223-32. 5. Parker *et al.* *Magn Reson Med* 2006;56:993-1000. 6. Li *et al.* *JMR* 2010;206:190-9. 7. Chen *et al.* *Radiology* 2011;258:821-31.

**Table 1. Mean  $\pm$  SD Values of BM DCE-MRI Parameters for CR and non-CR**

DCE-MRI Metrics	CR	non-CR
$K^{trans}$ ( $\text{min}^{-1}$ )	0.30 $\pm$ 0.13	0.54 $\pm$ 0.35
$v_e$	0.28 $\pm$ 0.17	0.22 $\pm$ 0.13
$k_{ep}$ ( $\text{min}^{-1}$ )	1.30 $\pm$ 0.53	2.14 $\pm$ 0.55

**Table 2. ULR  $c$  Statistics for Discrimination of CR and non-CR**

DCE-MRI Metrics	$c$ Statistics Value
Mean $k_{ep}$	0.90
Median $k_{ep}$	0.88
Mean $v_e$	0.70
Median $v_e$	0.68
Mean $K^{trans}$	0.68
Median $K^{trans}$	0.68

