Quantitative DCE-MRI as a Predictor of Acute Leukemia Response to Therapy

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Target Audience: Hematologic Oncologist, Radiologist, MRI Scientist

Purpose

Although it is increasingly recognized that acute myelogenous leukemia (AML) is a biologically heterogeneous disease, relatively few prognostic markers have been identified and the results of these laboratory studies are typically not available prior to the initiation of therapy in most patients. Consequently, there is a critical need to identify rapidly evaluable biomarkers associated with the most important therapeutic endpoint in AML, a complete remission (CR). Early identification of patients who are unlikely to respond to conventional chemotherapy would permit the rapid development of personalized therapeutic approaches for this high risk population while avoiding exposure to toxic and ineffective therapies.

Increased angiogenic activities have been observed in the bone marrow (BM) of AML patients (1), and correlations between higher 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 imaging modality for noninvasive evaluation of solid tumor response to therapy. A recent vertebral BM DCE-MRI study (3) shows that the pre-therapy Peak (maximum percent signal intensity change) measure is predictive of AML patient overall survival, demonstrating the utility of DCE-MRI for non-solid tumor studies. However, the Peak value is a semiquantitative measure. It is highly dependent on experimental 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 from a pre-therapy quantitative BM DCE-MRI study for the purpose of predicting CR following standard treatment of AML patients.

Methods

Nine newly diagnosed AML patients (5 males and 4 females; age: 49-64 years) consented to a research DCE-MRI study before undergoing standard induction chemotherapy. All the MRI scans 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 cm FOV, and 288x288 matrix size. Each DCE image volume set included 22 slices with 5 mm slice thickness, 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 ~ 10 min with a temporal resolution of 10 s. Gadolinium contrast agent (Prohance®) was administered (0.1 mmol/kg at 2 mL/s) through an antecubital vein following acquisitions of five baseline image volumes.

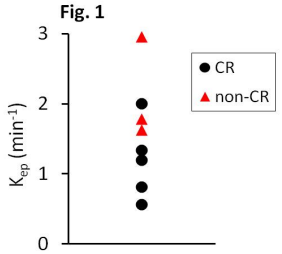
ROIs on multiple image slices were drawn encompassing vertebral bodies of L2, L3, and L4 as previously described (3), and also in left and right iliac crest. The ROI and pixel (within the ROI) DCE-MRI signal intensity time courses were then subjected to pharmacokinetic analyses (4) to extract K^{trans}, v_e, and k_{ep} (= K^{trans}/v_e) parameters. For the quantitative data analysis, 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^o, 10^o, and 20^o) 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. Histogram analyses of the pixel parameter values were performed for all the pixels of the five locations combined together.

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

DCE-MRI Metrics	c statistics value
Mean k_{ep}	0.867
Median k_{ep}	0.867
Mean v_e	0.733
Median v_e	0.733

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/non-response. The c statistics value produced by the ULR analysis is equivalent to the area under the curve (AUC) from the receiver operating characteristics (ROC) analysis.

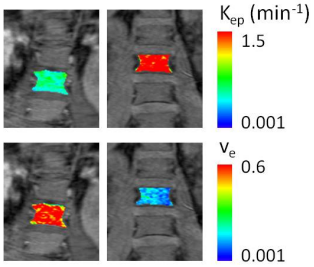
Fig. 1



Results

Among the nine patients, one deceased before remission status could be obtained, five achieved CR following therapy, and the other three had non-CR status. The **Table** shows that the BM mean k_{ep} and histogram median k_{ep} are good predictors of CR with c = 0.867, while the mean v_e and histogram median v_e are fair predictors with c = 0.733. **Fig. 1** shows a scatter plot of BM mean k_{ep} for the 5 CR and 3 non-CR patients. A cut-off value of 1.5 min^{-1} would have correctly classified all 3 non-CR patients, but misclassified 1 CR patient. **Fig. 2** displays the L3 k_{ep} (top) and v_e (bottom) maps superimposed on post-contrast DCE images from a typical CR (left) and non-CR (right) patients. The pre-therapy BM k_{ep} is generally lower and v_e higher for the CR compared to the non-CR patients.

Fig. 2



Discussion and Conclusion

As is demonstrated by the previous study (3), this preliminary study shows the utility of DCE-MRI as a noninvasive imaging method for evaluation of non-solid tumor cancer, such as leukemia. The initial findings suggest that the baseline (pre-therapy) intravasation rate constant k_{ep} is a good predictor of CR for AML patients undergoing standard induction chemotherapy. Since $k_{ep} = K^{trans}/v_e$ and K^{trans} was a poor biomarker for discrimination of CR from non-CR with c = 0.467 (results not shown), the high discriminative power of the k_{ep} parameter can most likely be attributed to the fact that the non-CR patients generally had lower v_e values than the CR patients, suggesting that the non-CR patients have higher baseline cancer cell density in the BM. Interestingly, the researchers who 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. Active enrollment of more subjects for this study is currently ongoing to validate the preliminary results.

Grant Support: NIH P30 CA069533, U01 CA154602.

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.