

Assessment of Early Vascular Response Under Abraxane Therapy Using DCE-MRI and ^{18}F -FPPRGD2 PET

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Purpose: The mechanism of action of Abraxane is complex, and some reports exist that Abraxane triggers reactionary angiogenesis. Our previous studies had shown some alterations of tumor vessels from immature to mature in morphological and molecular characteristics by Abraxane, and the integrin-specific PET tracer ^{18}F -FPPRGD2 (investigational new drug 104150) can noninvasive monitoring the integrin $\alpha_v\beta_3$ level. The purpose of this study is to further investigate a comprehensive vascular response (molecular level and functional such as permeability and penetration) during Abraxane therapy with combined dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and ^{18}F -FPPRGD2 PET.

Methods: Orthotopic MDA-MB-435 breast cancer mice were treated with Abraxane (25 mg/kg every other day, 3 doses) or phosphate-buffered saline. Tumor volume was monitored by caliper measurement. MR scans were obtained before and at different times after the start of treatment (days 0, 3, 7, 14, and 21) using DCE-MRI. ^{18}F -FPPRGD2 also was performed on the same time points to match with PET imaging. The tumoricidal effect was also assessed ex vivo by immunohistochemistry.

Results: Abraxane treatment inhibited the tumor growth, and a significant difference in tumor volume could be seen at day 5 after the initiation of treatment. The tumor uptake of ^{18}F -FPPRGD2 in the Abraxane-treated group was significantly lower on days 3 and 7 than at baseline but returned to the baseline level at days 14 and 21, indicative of relapse of the tumors after the treatment was halted (Figure 1). DCE-MRI measured a significant K^{trans} reduction on days 3 and 7 (Figure 2). Immunohistologic staining confirmed that the change of ^{18}F -FPPRGD2 uptake correlated with the variation of integrin level in the tumor vasculature induced by Abraxane treatment. The DCE-MRI K^{trans} change had an inverse correlation with the smooth muscle cells in vessel walls (Figure 3). Immunohistology suggested a vascular remodeling during Abraxane therapy.

Conclusion: Abraxane-mediated downregulation of integrin $\alpha_v\beta_3$ expression on tumor endothelial cells and upregulation of smooth muscle cells in vessel walls can be quantitatively visualized by DCE-MRI and PET. The change of integrin expression and smooth muscle cells precedes that of tumor size. Consequently, combined DCE-MRI and ^{18}F -FPPRGD2 PET provide reliable and supplementing biomarkers for assessing protein level and functional changes of Abraxane therapy response. The results of both methods are in excellent agreement with immunohistology. Furthermore, our results also indicate that vascular remodeling between Abraxane therapy.

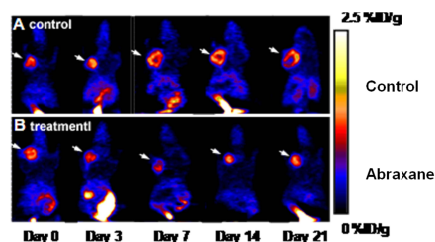


Figure 1. Representative decay-corrected whole-body coronal images of female athymic nude mice bearing orthotopic MDA-MB-435 tumors at 1 h after intravenous injection of ^{18}F -FPPRGD2 (3.7 MBq/mouse) on days 0, 3, 7, 14, and 21 after treatment was initiated. Decreased tumor uptake of ^{18}F -FPPRGD2 was observed on days 3 and 7 but was restored to baseline level on days 14 and 21. (A) PBS control. (B) Abraxane treatment.

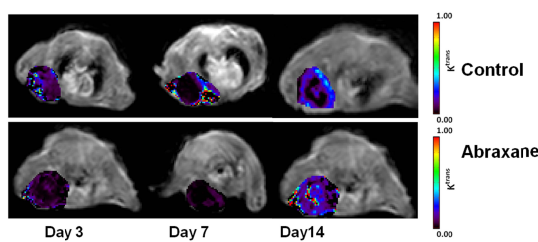


Figure 2. Representative axial images of female athymic nude mice bearing orthotopic MDAMB-435 tumors after intravenous injection of Gd-DTPA on days 3, 7, and 14 after treatment was initiated.

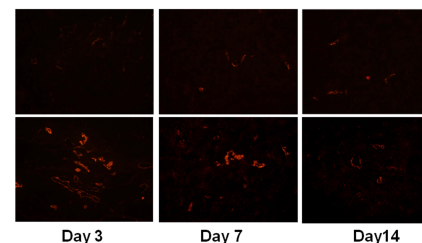


Figure 3. Staining of smooth muscle cell of tumor sections from PBS- and Abraxane-treated MDA-MB-435 tumors on days 3, 7, and 14.