Evaluation of vascular and metabolic response in a human breast cancer model treated with docetaxel

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Introduction

The anti-microtubule drug docetaxel is used in treatment of solid tumors like breast cancer, and is shown to have both cytotoxic and anti-angiogenic effects[1,2]. Clinical practice call for methods to evaluate treatment effects in breast cancer, in order to obtain individually tailored therapy. MRI and MRS are attractive methods for such purpose, and in this study, we evaluate the use of dynamic contrast-enhanced MR imaging (DCE-MRI), in vivo ^{1}H MRS and ex vivo HR MAS MRS of tissue samples as methods for detecting early treatment effects of docetaxel in a MCF7 mice xenograft model.

Experimental

MCF7 cells were implanted subcutaneously in athymic mice and treated with docetaxel (20, 30 and 40 mg/kg) or saline six weeks later. Tumor volumes were measured before and after treatment with digital calipers. Dynamic contrast enhanced (DCE) MRI and in vivo ^{1}H MRS were performed three days after treatment on a Bruker BioSpec 7T system. Pre-contrast T1-values were estimated based on a series of spin-echo (MSME) images with varying TR, followed by a series of T1-weighted images (MSME; TE=7ms, TR=200ms, FOV 20x20mm, matrix 64x64, slice 0.7 mm, n=100), where gadodiamide was injected during the 7th repetition. The dynamic images were used as input in a two-compartment model[3], to yield the perfusion parameters K^{trans} and v_e. Finally, a PRESS sequence was applied with TE=136ms and TR=2500ms to acquire in vivo MR spectra. Tumor tissue was excised and frozen in liquid nitrogen. HR MAS MRS was performed on a BRUKER Avance DRX600 spectrometer. The tumor biopsies were cut to fit a 50 µl MAS rotor, and deuterated buffer containing TSP was added. Single pulse acquired spectra were obtained with water presaturation. Both in vivo spectra and HR MAS spectra were used as input for partial least squares analyses (PLS) to compare controls to treated tumors.

Results and discussion

Tumor growth was suppressed in docetaxel treated mice compared to control. In addition, the antitumor effect altered the perfusion of the tumors, seen as increased K^{trans} values for the highest dose, and a trend to higher v_e values in all the treated groups (Fige A-F). This response pattern can be explained by a normalization of the vasculature in the tumor, together with reduced cell density and reduced interstitial fluid pressure[4]. Furthermore, changes in the tumor metabolism were seen with both in vivo MRS and ex vivo HR MAS MRS. PLS analysis of HR MAS spectra indicate relatively higher levels of phosphocholine and taurine in the controls, while the treated groups are dominated by metabolites as lactate, creatine, glycine and glycerophosphocholine (Fig G-H). Similarly, high levels of total choline and taurine for the controls was confirmed in the PLS of in vivo spectra (Fig I-J). The spectra from treated tumors have a more normalized metabolic pattern as compared to the controls, and this may be explained as inhibition of tumor cell proliferation and induced apoptosis. This treatment response has also been confirmed with ^{31}P MRS[5]. Immunohistochemical staining for proliferation, apoptosis and endhothelial cells is about to be analyzed in our lab.

Conclusion

In this study DCE-MRI, in vivo MRS and ex vivo HR MAS MRS has been used to demonstrate effects of docetaxel treatment on a model system of human breast cancer. Both changes in the perfusion and the metabolism were traceable.

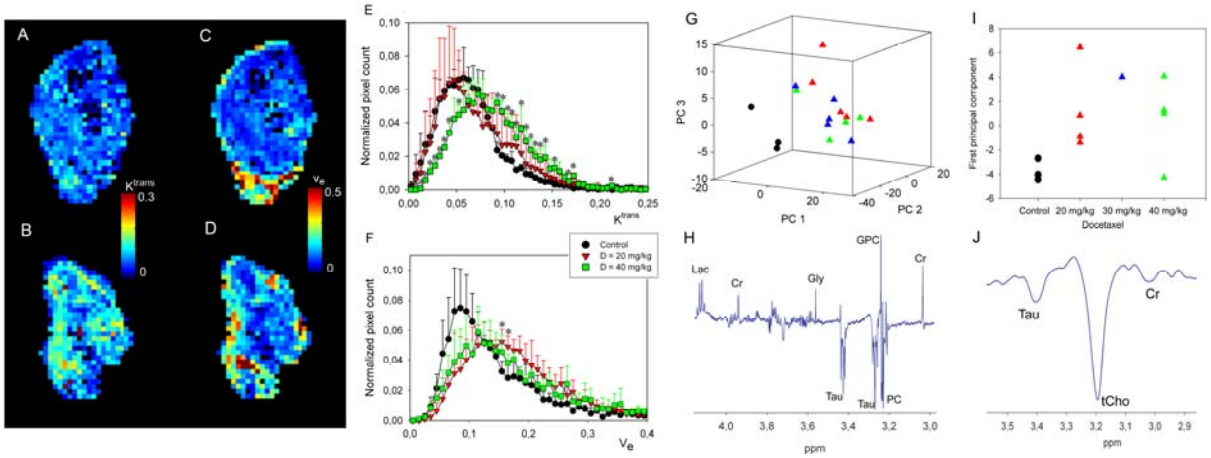

Figure: Parametric maps of K^{trans} and v_e for control tumor (A and C) and a treated tumor (B and D). Mean histograms for Ktrans (E) and ve (F). PLS of HR MAS spectra (G) with loading profile (H). PLS of in vivo spectra (I) with loading profile (J).

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