Evaluation of early response of docetaxel in MCF7 xenografts using ex vivo HR MAS MRS, in vivo MRS and DCE-MRI

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Introduction

Docetaxel (Taxotere) is an antitumor agent for treatment of patients with breast cancer. The drug induced polymerization of tubulin monomer leading to mitotic arrest in the cell cycle, and induces apoptotic cell death [(1)]. Recent clinical treatment strategies focus more on individualized patient protocols depending on the biological characterization of the tumors. To do so, sensitive methods for detecting early treatment response is highly needed. The purposes of this study were to 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

Xenografts were initiated by injecting MCF7 cells (10^7 cells) subcutaneously on the flank of the right hind leg on female BalbC/c nu/nu athymic mice. The tumor growth was measured with digital callipers. After 6 weeks, the mice were randomized into 4 different groups; a control group (n=5) and three groups treated with different doses of docetaxel (20 (n=4), 30 (n=2) and 40 (n=4) mg/kg). Short time after treatment (3-4 days) the tumors were examined with DCE MRI and in vivo MR spectroscopy. MRI experiments were performed on a BRUKER Biospec 7T horizontal bore magnet including measurement of precontrast T1-values using a series of T1-weighted spin-echo images, followed by a DCE-MRI series of 100 images with 12.8 sec temporal resolution. All tumors were imaged with three slices chosen axially and covered the largest tumor area with a voxel size of 0.39 x 0.39 x 1 mm^3. During the 7th repetition, a bolus dose of 0.1 mmol/kg Gd-DTPA-BMA, was injected intravenously. The mice were sacrificed and biopsies were cut from each xenograft and stored in liquid N_2. High resolution magic angle spinning MR spectroscopy (HR MAS MRS) was obtained using a BRUKER Advance DRX600 spectrometer (spin rate 5 kHz, 4 ºC). The DCE MRI data sets were analyzed pixel-by-pixel by use of in-house software developed in MATLAB. The signal enhancement curve for each tumor pixel was analysed to determine 1) the area under the enhancement curve during the 8 first minutes ($AUC_{0\text{-}8min}$), 2) the relative signal intensity (RSI) of each pixel in tumour region[(2)], 3) the 10% RSI percentiles, 4) Time to peak (TTP). In addition, K^{trans} and the volume fraction of EES (v_e) were estimated based on the Tofts model [(3)]. The HR MAS and in vivo spectra were normalized and VAST scaled [(4)] before multivariate principal component analysis.

Results and discussion

The HR MAS spectra showed small differences in the metabolic pattern of control tumors and docetaxel treated tumors (Fig. 1a). PCA analyses after VAST scaling gave a separation of control and treated tumors based on both HR MAS (Fig. 1b) and in vivo MRS (Fig. 1 c) spectra. No significant difference was found in the TTP, RSI or K^{trans} values for the two groups. There was no correlation between tumor growth after treatment and docetaxel dose during the observation time in this study. The differences in $AUC_{0\text{-}8min}$ and the volume fraction of EES (v_e) trend towards significance for control and treated tumors (p=0.052 for both). The two parameters correlated (r=0.98, p=0.01) and the treated tumors presented lower values of both parameters. These findings might reflect an increase in cell volume due to the docetaxel inhibition of tubulin depolymerisation leading to mitotic arrest in the G_2M phase of the cell cycle [(5)], causing a reduction in the EES.

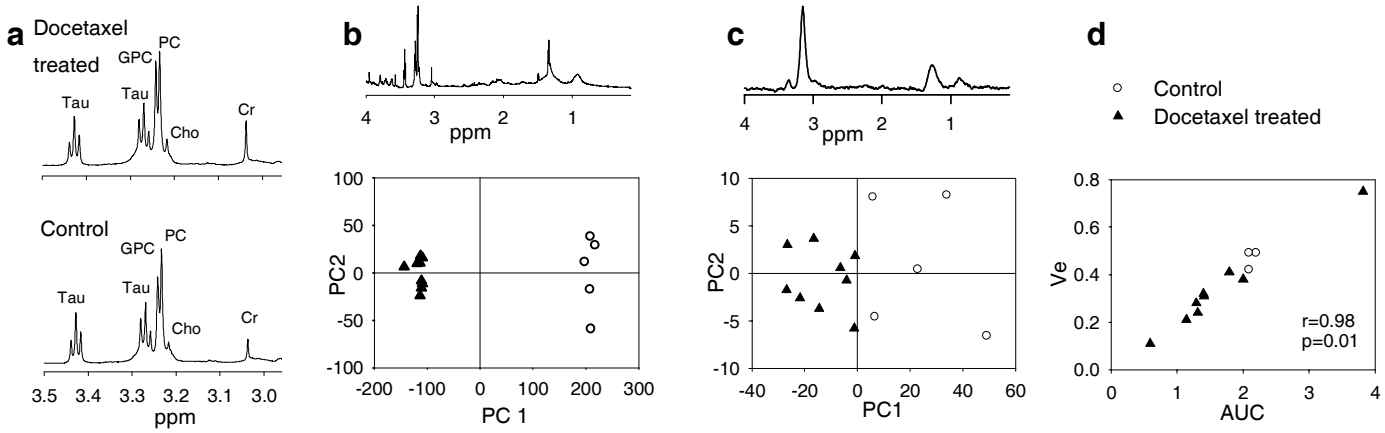

Figure 1: a) Mean HR MAS spectra of tumor tissue obtained from docetaxel (40 mg/kg) treated (n=4, upper spectrum) and control (n= 4, lower spectrum) MCF7 mice xenografts. The spectra contain glycerophosphocholine (GPC), phosphocholine (PC), taurine (Tau), choline (Cho) and creatine (Cr). The PCA score plot of all **b)** HR MAS samples and **c)** in vivo MRS spectra with a representative spectrum are shown at the top. **d)** The DCE-MRI derived parameters AUC and v_e correlate for control and treated animals. O Control tumors, % treated tumors.

Conclusion:

Combined HR MAS tissue metabolic profiles, in vivo MRS and DCE-MRI derived parameters can monitor early treatment changes of docetaxel in a MCF7 animal tumor model.

References:

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