Evaluation of early docetaxel effects in MCF7 xenografts using HR MAS, in vivo MRS, DCE-MRI and ADC-mapping

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Introduction

Docetaxel (Taxotere) is an antitumor agent used in treatment of patients with breast cancer. The drug induces polymerization of tubulin monomer leading to mitotic arrest in the cell cycle, causing 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 purpose of this study was to evaluate dynamic contrast-enhanced MR imaging (DCE-MRI), Apparent Diffusion Coefficient-imaging (ADC-mapping), in vivo ^{1}H MRS and ex vivo high resolution magic angle spinning (HR MAS) MRS of tissue samples for detection of early treatment effects of docetaxel.

Experimental

Xenografts were initiated by injecting MCF7 cells subcutaneously on the flanks of female BalbC/c nu/nu athymic mice. After 5 weeks, the mice were randomized into 3 groups: one Early Tumor Progression (ETP) (n=6), treatment control (n=8) and docetaxel treated (n=8). The ETP mice were sacrified at the day of randomization, and the biopsies were stored in liquid N_2. One week later the two latter groups were treated with docetaxel (30 mg/kg) or saline (15 ml/kg).These two groups were examined with DCE MRI, ADC mapping and in vivo MR spectroscopy 3 and 6 days after treatment. MRI was performed on a BRUKER Biospec 7T scanner. Precontrast T1-values were measured using a series of T1-weighted spin-echo images, followed by a DCE-MRI series of 200 images with 4.8 sec temporal resolution and a voxel size of 0.16x0.16x0.7 mm^3. During the 10th repetition, a dose of 0.1 mmol/kg Gd-DTPA-BMA (Gadiodiamide), was injected intravenously. ADC maps were obtained from 5 different b- values (0, 100, 300, 600, 1000). In vivo MRS volumes were located within the tumor (3x3x3 mm^3) and obtained using the PRESS sequence (TE=20 msec, TR=3000 msec). All mice were sacrificed after MRI at day 6 and biopsies were stored in liquid N_2. HR MAS MRS was obtained using a BRUKER Avance DRX600 spectrometer (spin rate 5 kHz, 4 ºC). The signal enhancement curve for each voxel was analysed (MATLAB) to determine 1) the area under the enhancement curve during the 2 first minutes ($AUC_{0\text{-}2min}$), 2) the relative signal intensity (RSI) of each voxel in the tumor region[(2)], and 3) 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 peak aligned, baseline offset corrected and normalized before multivariate Partial Least Squares (PLS) analyses.

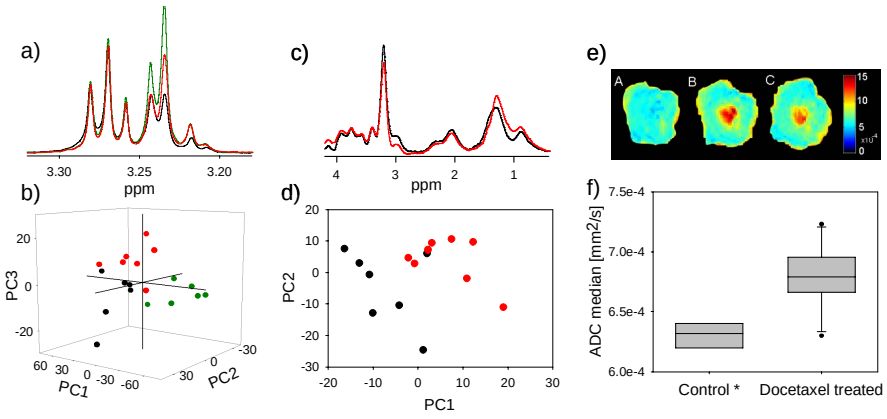

Figure1. a) Mean HR MAS spectra from docetaxel treated (n=7, red), treatment control (n=6, black) and ETP (n=6,green) shows that the choline level changes during tumor progression and after treatment. **b)** PLS of the HR MAS spectra shows clustering in a 3D PC plot. **c)** Mean in vivo MRS spectra from docetaxel treated (n=8, red) and treatment control (n=7, black). The spectra shows that docetaxel treated tumors have a slightly higher level of lipids and lower level of cholines. PLS score plot of these spectra **d)** shows a clustering of the two groups. **e)** ADC map of a tumor 1 day before, 3 and 6 days after docetaxel treatment. **f)** The ADC medians after treatment for the docetaxel treated tumors (n=10) were significant (p=0.002) different from the treatment controls(n=6) as shown in the boxplot.

***One animal were excluded due to extreme high ADC values.

Results and discussion

The HR MAS spectra showed distinct differences in the metabolite profile of control tumors, docetaxel treated tumors and ETP group. The ETP group had a higher level of total Choline (tCho) than both the control group and docetaxel treated group. The control group obtained a lower level of tCho and the ratio between phosphocholine (PC) and glycerophosphocholine (GPC) was substantially reduced. The docetaxel treated tumors conserve the high PC/GPC rate but obtain a lower level of tCho (Fig. 1a). This might indicate that the tumors after docetaxel treatment change towards a metabolite profile more similar to an earlier stage of progression. The score plot from PLS give a significant separation of all three groups (Fig. 1b). The in vivo MRS spectra indicate small differences in the metabolite profile of controls compared to docetaxel treated tumors (Fig. 1c). Distinct clusters can be observed in the score plots (Fig. 1d), and the loading profiles indicate a lower level of tCho and a higher level of lipids in the treated tumors. The tumors had a significant increase in water diffusion coefficient (p=0.002) in response to treatment (f). This is in accordance with earlier findings [(4)]. No significant difference was found in the K^{trans}, v_e, RSI , AUC and TTP values or distribution of this values, analysed by multivariate data analysis, for the two groups. This lack of significance might be due to insufficient changes in tumor vasculature in this study. Such results has also been observed previously [(5)].

Conclusion:

Our findings shows that HR MAS MRS, in vivo MRS and ADC in tumors can monitor changes during tumor progression and treatment response caused by docetaxel in tumor tissue.

References:1) Marchettini P. Cancer Chemother Pharmacol, 2002, 49:499-503, 2) Mayr NA et al. J.Magn Reson.Imaging, 2000, 12:1027-1033, 3)Tofts PS et al. J.Magn. Reson. Imaging, 1999, 10:223-232, 4) Su MY et al. Technol Cancer Res Treat, 2002, 1:479-88, 5)Jennings D. et al. Neaplasia, 2002,4:255-262.