Multiparametric MRI/MRS and gene expression profiling for monitoring docetaxel effects in MCF7 xenografts

E. M. Huuse[1], L. R. Jensen[1], P. E. Goa[1,2], S. Lundgren[1,3], E. Anderssen[4], T. F. Bathen[1], and I. S. Gribbestad[1]

[1]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, [2]Department of Radiology, St. Olavs University Hospital, Trondheim, Norway, [3]Department of Oncology, St. Olavs University Hospital, Trondheim, Norway, [4]Department of Cancer Research and Molecular Medicine, NTNU, Trondheim, Norway

Introduction

Several methods are candidates for detecting early response in breast cancer patients undergoing chemotherapy. Docetaxel is an antitumor agent that induces polymerization of tubulin monomer leading to mitotic arrest in the cell cycle, causing apoptosis and cell death through mitotic catastrophe(1). The purpose of this study was to evaluate the sensitivity of contrast enhanced MR imaging (DCE-MRI), diffusion MRI, in vivo MRS and gene expression profiling for detection of small effects early after docetaxel treatment.

Experimental

Xenografts were initiated by injecting MCF7 cells subcutaneously on the flanks of female BalbC/c nu/nu athymic mice. Tumor volume was measured with a digital calliper during growth. After five weeks, the animals were randomized into two groups, one treated with docetaxel (30 mg/kg, n=6) and controls given saline (15 ml/kg, n=5) intra peritoneal. Tumors were examined with DCE-MRI, ADC mapping and in vivo MR spectroscopy 1 day before and 1, 3 and 6 days after treatment using a BRUKER Biospec 7T scanner. Precontrast T1-values were measured using a series of T1-weighted spin-echo images with varying TR, followed by a DCE-MRI series of 200 images with 4.8 sec temporal resolution and a voxel size of 0.32x0.32x0.7 mm^3. During the 10^{th} repetition, a dose of 0.1 mmol/kg Gd-DTPA-BMA (Gadiodiamide), was injected intravenously (4 sec). ADC maps were obtained from diffusion weighted MRI with 5 different b-values (0, 100, 300, 600, 1000 sec/mm^2). In vivo MRS volumes were localized within the tumor (3x3x3 mm^3) using the PRESS sequence (TE=20 msec, TR=3000 msec). All mice were sacrificed after the MR examination at day 6 and biopsies were stored in liquid N_2. The signal enhancement curve for each voxel was analysed (MATLAB) to determine the relative signal intensity (RSI) for each voxel in the tumor region, K^{trans} and v_e based on the Tofts model(2). Voxels with RSI lower than 80% at one minute post injection were excluded(3). In vivo spectra were peak aligned, baseline offset corrected and normalized before multivariate Partial Least Squares (PLS) regression analyses. RNA was extracted and gene expression profiles were obtained by illumina arrays. Data were log(2) transformed and quantile normalised before multivariate PLS regression analyses.

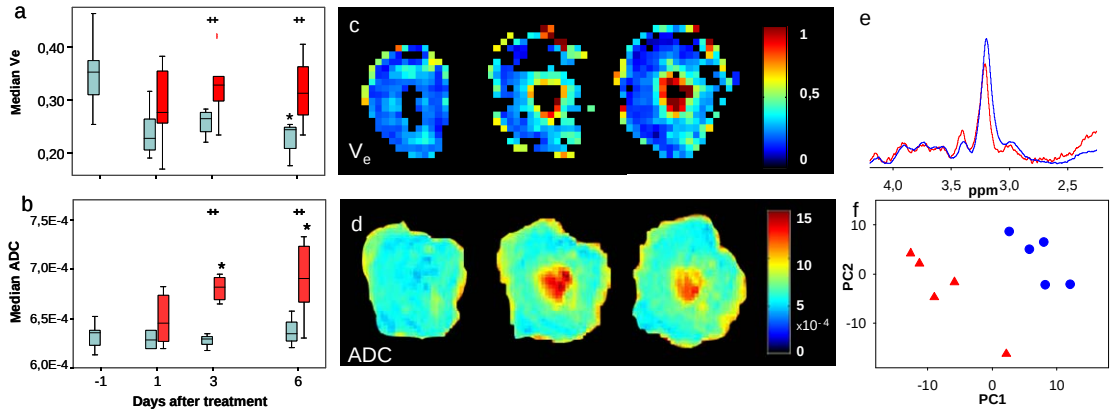

Figure 1:a,b) Boxplots of V_e and ADC in control (blue) and treated (red) tumors 1 day before treatment, 1, 3 and 6 days after treatment respectively. * significant different (Dunnet) compared to before treatment (-1), and ++ significant difference (t-test) between treated and control the particular day. **c,d)** Ve and ADC maps from same tumor one day before treatment, 3 days and 6 days after treatment. **e)** Two representative in vivo MRS spectra from a control (blue) and a treated tumor (red) three days after treatment. **f)** PLS score plot of gene expression data shows a clear clustering of the two groups (●=control, ▲= treated).

Results and discussion

There was not observed any difference in tumor growth between the two groups during the 6 days after treatment, which might indicate a small treatment effect. The tumors had, in accordance with earlier findings(4) a significant ($p<0.03$) change in median ADC 3 and 6 days after treatment compared to the control group and to values before treatment (Fig. 1b). No significant difference was found in the K^{trans}, however, median v_e was significant higher ($p<0.04$) in treated tumors at day 6 (Fig. 1a). The changes in ADC and v_e could be a result of inhibitation of cell proliferation and cell death in treated tumors. The lack of changes in K^{trans} might be due to only indirect effects on tumor vasculature, induced by docetaxel. The in vivo MR spectra showed a slightly lower level of total choline signal in docetaxel treated tumours compared to controls (Fig. 1e). Both for in vivo MRS and gene expression data, treated tumours and controls were clearly separated in different clusters by PLS analysis (Fig. 1f), suggesting a genetic and metabolic change due to docetaxel treatment.

Conclusion:

Our findings shows that multiparametric MRI, based on DCE-MRI and diffusion MRI, in vivo MRS and gene expression profiles can monitor small changes during breast treatment response caused by docetaxel in MCF-7 xenografts.

References:1) Morse DL. Mol Cancer Ther 2005 Oct;4(10):1495-504, 2)Tofts PS et al. J.Magn. Reson. Imaging, 1999, 10:223-232, 3) Kuhl CK. Radiology 1999 Apr;211(1):101-10, 4) Jennings D. et al. Neoplasia, 2002,4:255-262.