Detecting Early Tumor Response to Chemotherapy Using in vivo 1H MRS

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Introduction

The choice of drug to treat an individual's cancer is a critical decision oncologists must make, often with only limited information about the tumor microenvironment and metabolism. Tumor markers, such as the over-expression of the HER2 proto-oncogene and estrogen receptor in breast cancers, have predictive value for the selection of adjuvant treatments (1). However, these tumor markers do not directly address the dynamics of tumor response. Success in customizing treatments for achieving maximum benefit requires a means to detect a response to the drug early in the course of treatment. *In vivo* ^{1}H MRS measurement of total choline-containing compounds (tCho) may provide valuable information about membrane choline phospholipid metabolism that relates to proliferative activity. Accordingly, the level of tCho and the changes in tCho levels following treatment may be used to predict and monitor anti-proliferative activity of drugs. In this study, we employed a xenograft tumor model in which each mouse harbored both doxorubicin-sensitive and resistant tumors. Response was monitored by quantitative tCho measurements using single-voxel spectroscopy.

Methods

Both wild-type MCF-7 cells (MCF-7/WT) and the doxorubicin-resistant cell line (MCF-7/AdrR) were injected to induce xenograft tumors in the right and left mammary fat pads of the same athymic mice. Estrogen pellets were implanted on the back of animals for optimal growth of tumor cells. When tumors reached a volume of about 0.5 cm^3, MRI and MRS were performed to measure baseline tCho levels. For quantification, a fully relaxed, unsuppressed water spectrum from the same voxel was also acquired. tCho signal was referenced against the measured tissue water signal in each voxel. For MR studies, mice were anaesthetized with 0.25ml/100g of 1:1:4 mixture of acepromazine (10mg/ml), xyline (20mg/ml) and ketamine (100 mg/ml) and maintained under physiological conditions. Experiments were performed at 4.7 tesla using a 1.2 cm transceive surface coil. Tumors were visualized using 3D FLASH. Localized ^{1}H spectroscopy was performed with the LASER technique, using water suppression, TR = 3 s, TE-averaging (TE = 30 - 183 in 128 increments) (2), and voxel sizes ranging from 20 - 64 μl.

The day after baseline measurements were performed (day 0), 8 mg/kg of doxorubicin was injected intraperitoneally. Control mice received a similar amount of phosphate buffered saline. The signal ratios (tCho/water) from the same voxels in both doxorubicin-sensitive and resistant tumors were measured again approximately 24 and 48 hours after injection.

Results

Figure 1 shows a coronal image of both MCF-7/WT and MCF-7/AdrR tumors in the same animal and their spectra. Before doxorubicin treatment, average tCho/water ratios were 903 ± 151 (mean ± SD, n=5) and 848 ± 119 from MCF-7/WT and MCF-7/AdrR tumors, respectively. There was not a significant difference in the baseline tCho/water ratios between MCF-7/WT and MCF-7/AdrR tumors ($p > 0.05$). The control group treated with phosphate buffered saline exhibited no significant change in tCho/water in either tumor types ($p > 0.05$). However, as shown in Figure 2, sensitive MCF-7/WT tumors responded with a marked decline in tCho/water (68 ± 6 % of control, $p < 0.005$) by 24 hours after drug administration, whereas MCF-7/AdrR tumors showed a smaller decrease (87 ± 12 % of control) which did not reach statistical significance ($p > 0.05$). The tCho/water ratio in MCF-7/WT tumors declined further to 50 ± 6 % of control by 48 hours, whereas the ratio in MCF-7/AdrR tumors remained similar to the 24 hour level (85 ± 9 % of control).

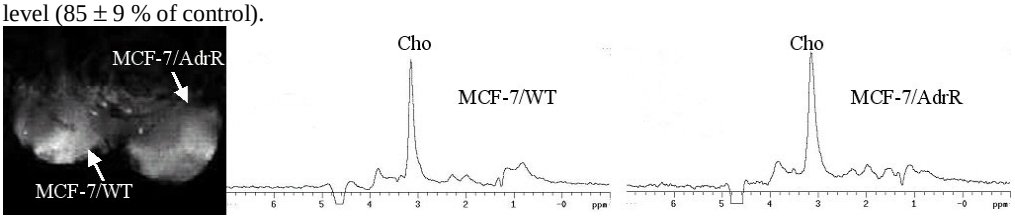

Fig. 1. Coronal image of both MCF-7/WT and MCF-7/AdrR tumors grown in the mammary fat pads of a single mouse and their spectra before treatment.

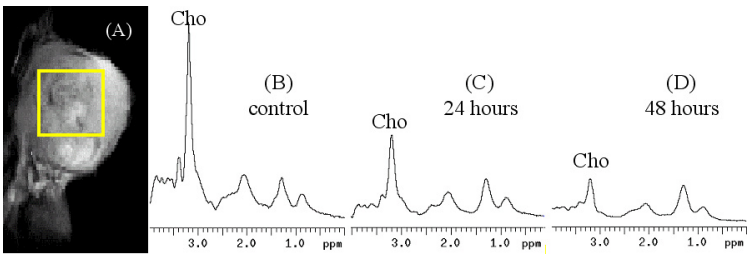

Fig. 2. (A) Single voxel in sagittal image of MCF-7/WT tumor in the mammary fat pads of an athymic mouse and the corresponding spectra before (B), ~24 hours (C) and ~48 hours (D) after administration of 8 mg/kg doxorubicin i.p.

Discussion

It has been reported that chemotherapeutic doxorubicin localizes in acidic intracellular organelles in drug-resistant cells but is dispersed throughout the cytoplasm and nucleus in drug-sensitive cells (3). The differential responses of tCho levels in doxorubicin-sensitive tumors and doxorubicin-resistant tumors are in agreement with previous studies showing that tCho offers the capability to monitor response to chemotherapy. The present study shows that 24 hours after doxorubicin is long enough to detect early response *in vivo* using the change in tCho levels, when the tumors are sensitive to the drug. The xenograft model with both sensitive and resistant tumors in the same animals appears to provide a potent tool to confirm early detection of tCho changes in chemo-sensitive tumors.

References

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