In vivo Monitoring Therapeutic Response of NHL Xenograft by MRS and MRI

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Introduction

The worldwide incidence of non-Hodgkin's lymphoma (NHL) continues increasing so that it becomes one of the most common causes of cancer death. However, only a third of NHL is currently curable by standard chemotherapy. Availability of effective noninvasive methods for predicting or/and detecting the response of NHL to therapy would be of important clinical interest. It would facilitate the rational design and optimization of the therapy protocols at the first place. A multi-institutional clinical trial has recently demonstrated that pre-treatment 31P MRS of non-Hodgkin's lymphoma (NHL) tumors identifies ~2/3 of the patients that fail to exhibit a complete response to chemotherapy, which suggested that ^{31}P MRS can predict the response of NHL patients to chemotherapy. However, the low sensitivity of ^{31}P MRS limits its clinical application. In vivo tracking the longitudinal response of human tumors to therapies in clinical remains challenging. While, the mouse tumor model of human cancer allows us to follow the therapeutic response of the tumor, which would guide therapy for better therapeutic efficiency. Diffuse large cell lymphoma (DLCL2) is the most common subtype of NHL. In this study, we have evaluated the therapeutic response of DLCL2 xenograft in SCID mice to chemotherapy by MRS and MRI. MRS detects global therapeutic response of the tumors; while, MRI supplies regional parametric maps and detects local response.

Methods and Materials

DLCL2 tumors were subcutaneously implanted in the upper thighs of 6-8 week old female SCID mice by inoculating 1.0×10^7 DLCL2 cells. Five mice were treated with four cycles of CHOP and bryostatin 1 (CHOPB), which was used to inhibit expression of the mdr1 gene for better therapeutic response [1]. Control mice were sham treated. MRS and MRI were performed with 9.4 T and 4.7 T magnets, respectively two days before treatment and once a week after completion of each cycle for four cycles. A non-localized selective multiple-quantum coherence transfer sequence [2] was employed to detect the global lactate signals from the tumor. Non-localized ^{31}P MRS was performed to evaluate phospholipid metabolism. In diffusion-weighted MRI, a multi-slice spin-echo sequence with bipolar-pulsed gradients applied in three orthogonal directions was employed at four b-values in the range of 0-118 s/mm^2. TR and TE were 2 s and 60 ms, respectively. A multi-slice spin-echo imaging sequence was employed in T_2-weighted MRI with four values of TE from 15 to 75 ms and TR of 2.0 s. ADC maps and T_2 maps were produced by a pixel-by-pixel fitting. Histological analysis was finally carried out on the tumor tissue.

Results and Discussions

The tumor volumes in the CHOPB treated group decreased to about 60% of the pre-treatment values, while the volumes of the control tumors increased monotonically (Fig. 1a). The lactate (Fig. 1b) in ^{1}H MR spectra and the PME/bNTP ratios (Fig. 1c) in ^{31}P MR spectra of the tumors in the CHOPB treated animals began to decrease approximately one week after the first cycle of treatment; while, these levels of the untreated control tumors increased slightly. Fig. 2 presents the T_2 maps (upper row) and ADC maps (lower row) of control tumors (a and b) and CHOPB treated tumors (c and d). The a and c maps were measured before the first cycle of the treatment, whereas the b and d maps were acquired after two cycles of the treatment. Both T_2-maps and ADC-maps indicate more heterogeneity in the CHOPB treated tumors after two cycles of CHOPB. Fig. 3 presents the time course of (a) the average T_2 and (b) average ADC of the control tumors and of CHOPB treated tumors. The average ADC shows a significant increase in the treated tumors after two cycles of CHOPB, but decreases in the control tumors. The average T_2 of the treated tumors decreases significantly after two cycles of CHOPB; while the average T_2 of control tumors shows no significant change. Fig. 4 presents the H & E histology of (a) a control and (b) treated tumor. The treated tumor shows more heterogeneity than the control tumor, which conformed the discovery of both T_2-weighted and DW MRI. The cell density of the treated tumors appears lower than that in the control tumor as indicated in Fig.4. The lower tumor cell density in the treated tumors could be accompanied with higher proton density. It may contribute to the ADC difference between the control and treated tumors. The higher proton density results in stronger spin-spin interaction and shorter T_2 in the treated tumors. Another reason for the shorter T_2 may relate to the heterogeneity of the treated tumors, which caused more magnetic inhomogeneity in the treated tumors, and as a result, a shorter T_2.

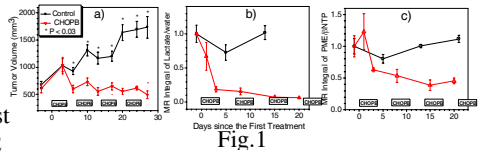

Fig.1

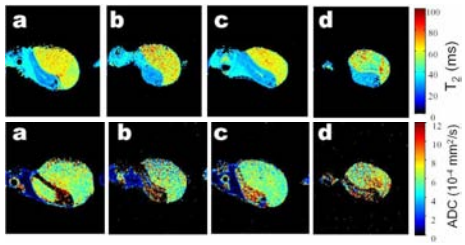

Fig.2

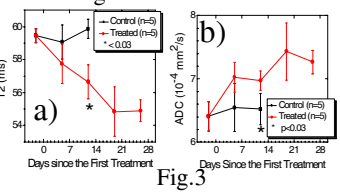

Fig.3

Conclusions

Our study strongly suggests that the combination of MRS and MRI are sensitive to *in vivo* therapeutic response of NHL tumors. Lactate may be a global therapeutic marker for NHL. Both T2 and ADC are potential clinical markers of regional therapeutic response. Further studies of DCE MRI are in progress.

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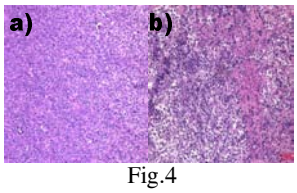

Fig.4

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2. He, Q et al., *J. Magn. Reson. Ser. B,* 1995. **106**: 203-211.