Monitoring Response to Convection-enhanced Taxol Delivery in Brain Tumor Patients Using Diffusion-weighted Magnetic Resonance Imaging

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Introduction

Recurrent malignant primary brain tumors are usually fatal within months of diagnosis of recurrence. Chemotherapy confers no significant survival advantage, in part because of the poor penetration of most chemotherapeutic drugs across the blood brain barrier and into the tumor. CEDD1 is a novel approach to deliver drugs directly into brain tumors (1). It is based on delivering continuous small pulses of drug via an intratumoral catheter, leading to convective distribution of the drug within the tumor. Paclitaxel (Taxol) is a potent antineoplastic agent that is effective against brain tumors in vitro but does not cross the blood brain-barrier. Accordingly, it was a good candidate drug for this mode of therapy. A Phase I-II clinical trial was designed to deliver Taxol by intratumoral convection-enhancement in patients with recurrent malignant brain tumors.

To monitor the effects of convection-enhanced Taxol delivery, we have used DWMRI. This technique enables noninvasive assessment of biological tissues based on their water diffusion characteristics. It has been shown that there is an order of magnitude difference between the diffusion of slow/intracellular and fast/extracellular water molecules in vitro (2–3). Therefore, it is anticipated that DWMRI will detect early changes in morphology and physiology of tissues associated with changes in water content such as changes in the permeability of cell membranes, cell swelling, and cell lysis.

DWMRI has only recently been applied for early detection of response to anticancer therapy (4–9). In this work, we have demonstrated the feasibility of using line-scan DWMRI (10) as a noninvasive tool to continuously monitor the progression of the convection process and its effect on the treated tissue.

Materials and Methods

Equipment and Software. Data were acquired using a GE 0.5T interventional MRI machine (Signa SP) at the Chaim Sheba Medical Center and the standard GE birdcage head-coil. Image analysis was performed on a Pentium III personal computer using the Interactive Data Language (IDL) software package (version 3.6.1), Research Systems Inc.

Diffusion-weighted MRI Method. Application of a pair of pulsed magnetic field gradients sensitizes MR experiments to molecular diffusion/motion (11). In this method, the normalized intensity of the water signal is given by:

\[ I/I_0 = \exp[-γ^2δ^2(\Delta - δ/3)ADC] = \exp[-b \cdot ADC] \]  

where \( I \) and \( I_0 \) are water signal intensities in the presence and absence of diffusion-sensitizing gradients, respectively; \( γ \) is the gyromagnetic ratio of the nucleus; \( g \) and \( δ \) are gradient strength and duration, respectively; \( (\Delta - δ/3) \) is the effective diffusion time; \( ADC \) is the ADC; and \( b \) is the diffusion weighting factor, which is expressed in units of s/mm².

Patients and Treatment. Three patients with recurrent malignant glioma received intratumoral convection-enhanced Taxol (1 mg/ml), continuously administered for several days at a rate of 5 μl/min. Patient 1 was treated for 5 days. Patient 2 was treated for 3.5 days. Patient 3 was treated for 2 days.

Imaging. Line-scan DWMRI and contrast-enhanced T1-weighted (T1-Gd) and T2-weighted MRI were used to monitor the patients daily, before, during, and following treatment. All of the images were acquired with 4-mm slices, two signal averages, and a 22 × 16-cm field of view. T2-weighted MRI were acquired with a 256 × 128 matrix, TR = 3000 ms, and TE = 1995 ms. T1-weighted MRIs were acquired with a 256 × 128 matrix, TR = 500 ms, and TE = 14.5 ms. DWMRIs were acquired with a 128 × 64 matrix, \( b = 1000 \) s/mm², \( Δ = 31 \) ms; \( Δ = 51 \) ms; TR = 2907 ms, and TE = 105.2 ms.

Diffusion Gradient Scheme. In normal white matter the diffusion of the water molecules is anisotropic and data must be acquired in three orthogonal directions and then averaged to obtain isotropic diffusion coefficients. In this work, data were acquired using a monodirectional diffusion scheme (described in detail in Ref. 10), because of the long acquisition times at 0.5T. This measurement should suffice because of the natural anisotropy of cancer tumors and the reasonably reproducible head orientation.

Diffusion Parameters. The water ADCs presented in Fig. 1 were calculated from the mean signal intensities of regions of interest chosen in the DWMRI images acquired at \( b = 5 \) s/mm² and at \( b = 1000 \) s/mm², using Eq. A.

Results and Discussion

The three MRI methods applied gave different results (Figs. 2 and 3): (a) T2 images showed no consistent pattern of response in the first week after therapy began; (b) T1-Gd images showed the treated area as a centrally nonenhancing region surrounded by an enhancing rim. The size of the enhancing rim increased over time. The contrast enhancement varied from scan to scan, but the general pattern was consistent; (c) DWMRIs showed clear changes in water diffusion within the first 24–48 h after the treatment was begun. The shape,
magnitude, and nature of this effect changed continuously over time. The initial effect was the appearance of a bright area. Subsequently, while the bright area continued to spread, a dark area appeared within it (Fig. 2). The response to the treatment was clearly detected in the DWMRIs at least 1 or 2 days before it could be detected by the conventional imaging methods.

The T1-Gd images showed a well-defined spatial definition of the spread of the convection-treated area in all cases. However, there was no significant change in terms of tissue contrast within the nonenhancing region during the treatment, and there was no significant difference between the patients. In the DWMRIs, on the other hand, there were clear changes in contrast in the treated area (Figs. 2 and 3), and there was variation among the patients. This variation is demonstrated in Fig. 4, where the maximum effect of the dark area in each patient is shown. In all of the patients, the early response to the treatment (24–48 h after treatment began) appeared as a bright region. In the DWMRI of patient 1, a dark area appeared within 2–4 days. In a T1-Gd image acquired 2 weeks posttherapy (Fig. 2), it can be seen that the treated area changed into a large dark region, perhaps reflecting the long period of treatment (5 days). Patient 2 showed a dark area similar in intensity to that of patient 1, appearing only 19 days after treatment (Fig. 4). The response of patient 3, who received only 2 days of treatment, as demonstrated by DWMRIs did not change (remained bright) over time (>4 weeks) despite T1-Gd hypointensity (Fig. 3). Whether the persistence of the DWMRI hyperintensity in the presence of T1-Gd hypointensity indicates viable tumor is yet unknown.

The changes in the water ADC values as a function of time for the three patients are shown in Fig. 1. We speculate that the high initial

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**Fig. 1.** ADCs as a function of time for the three patients. ADCs were calculated from data acquired at $b = 5$ and 1000 s/mm$^2$.

**Fig. 2.** MRIs of one slice in the treated area of patient 1. Time is counted from the initiation of the treatment. Top, T2-weighted MRI; middle, T1-Gd; bottom, DWMRI acquired with $b = 1000$ s/mm$^2$.

**Fig. 3.** MRIs of one slice in the treated area of patient 3. Time is counted from the initiation of the treatment. Top, T2-weighted MRI; middle, T1-Gd; bottom, DWMRI acquired with $b = 1000$ s/mm$^2$.

**Fig. 4.** MRIs of one slice in the treated area of patient 1. Time is counted from the initiation of the treatment. Top, T2-weighted MRI; middle, T1-Gd; bottom, DWMRI acquired with $b = 1000$ s/mm$^2$. 
ADC value in all three of the patients is attributable to necrosis observed in malignant gliomas. Once the treatment has begun, the ADCs decreased in all of the patients. Assuming the slow component is correlated with intracellular water, this change can be explained by cell swelling, perhaps attributable to the effects of Taxol. It cannot be ruled out that other factors, such as localized changes in the blood-brain barrier permeability, have contributed to this effect, although the absence of changes in the T1-Gd images are not consistent with such an explanation. In two patients, there was a subsequent increase in the ADCs. This change appeared sooner and was more pronounced in patient 1, in agreement with the presumed effective response to the therapy. One explanation for the dark area may be accumulation of drug-induced necrosis. In patient 1, at 2 weeks posttherapy, most of the treated tissue has become very dark in the T1-Gd image (Fig. 2, right), and this dark region may represent almost complete tumor response to Taxol. Fig. 1 demonstrates the additional information that can be obtained from DWMRIs, i.e., the identification of a response pattern (such as an initial decrease in ADC, followed by a later increase) and its correlation with the time-scale of tissue changes in different patients.

In conclusion, this is the first report of the application of DWMRI for noninvasive monitoring of CEDD into brain tumors. DWMRI enables the observation of early changes in water diffusion in tissues. These changes in brain images after therapy are not observed by conventional MRI methods.

We have shown that DWMRI provides early information on the extent and effect of the convection wave and additional tissue characterization. The differences in diffusion characteristics among the three patients suggest that this technique might enable the distinction between different response rates of different patients.

We are continuing the experiments and are comparing the values of the ADCs from these studies with the results seen with other central nervous system pathologies to further elucidate the origin of these phenomena.

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References

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