MRI Study of Chemotherapeutic Effects in Subcutaneously Implanted 9L Glioma Tumors

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Introduction

According to recent reports (1,2), it appears that increases in both the apparent diffusion coefficient (ADC) of water and $[Na^+]$ in the tumor ($[Na^+]_{tumor}$) after chemotherapy are correlated, which suggests that this may be a general response of tumors to many anticancer drugs. However, the response of tumors to therapy depends on many different factors, including tumor location, degree of tumor vascularization, vascular permeability (blood-brain barrier), degree of hypoxia in the tumor, and drug metabolism and pharmacokinetics (3). In this study, we investigated the effects of the anticancer drug 1,3-bis(2-chlorethyl)-1-nitrosourea (BCNU) on water ADC measured by ^1H MRI and $[Na^+]_{tumor}$ measured by ^{23}Na MRI in subcutaneously- (sc-) implanted 9L glioma. Our goal was to determine if the increase in water ADC and $[Na^+]_{tumor}$ after chemotherapy is a general phenomenon.

Methods

Fifteen tumor-bearing rats were treated with a single dose of BCNU (25 mg/kg, ip, Sigma-Aldrich, St. Louis, MO), and six animals served as untreated controls. MRI measurements were performed one day prior to treatment with BCNU, and on days one, three, and five after treatment. Control animals were studied at corresponding time points without BCNU treatment. All MRI experiments were performed on a 9.4 Tesla 31-cm horizontal bore system (Varian, Palo Alto, CA) equipped with a 12-cm diameter shielded gradient set capable of up to 40 G/cm in three directions. A loop-gap resonator (inner diameter = 30 mm, depth = 25 mm) dual tuned to 400 MHz for ^1H and 106 MHz for ^{23}Na was used. 3D transaxial ^{23}Na MR images of the tumor were obtained with a gradient-echo imaging sequence using the following parameters: 100 μs non-selective excitation RF pulse, 50 ms repetition time (TR), 10 ms echo time (TE), 64 x 32 x 8 data points over a 40 x 40 x 36 mm field of view (FOV). Water ADC images of the tumor were obtained with a multi-slice diffusion-weighted imaging (DWI) sequence using the following parameters: 1,100 ms TR, 10 ms TE, 256 x 128 data points over a 40 x 40 FOV, 2.0 mm slice thickness, 0.6 mm slice gap, and four interleaved b-factors (b= 0, 236, 945, and 1,679 s/mm^2). ^1H images and water ADC maps were reconstructed using the Image Browser software provided by Varian.

Results and Discussions

Treated animals were divided into two groups according to their response to BCNU: BCNU-responsive (BCNUrsp) and BCNU-nonresponsive (BCNUnrsp). In the BCNUrsp group, tumor growth was arrested for the duration of the experiments (5 days) after BCNU injection, indicating effective tumor cell killing. In the BCNUnrsp and untreated control groups, the mean tumor volume increased 135-145% by day five (**Fig. a**). BCNUrsp tumors initially had significantly higher ADC than both BCNUnrsp and untreated tumors (**Fig. b**, Day -1). In the control group, water ADC increased constantly during the experimental period. A similar trend was seen in the BCNUnrsp group. The mean ADC values in both groups increased ~1.6 times by day five post-treatment. In contrast, the BCNUrsp group showed a slight decrease in the mean ADC five days post-treatment (**Fig. b**). The changes in $[Na^+]_{tumor}$ were very similar to the changes in water ADC. The pretreatment ^{23}Na MRI signal intensity (compared to an external reference) was lowest in the BCNUnrsp group and highest in the BCNUrsp group (data not presented). After BCNU treatment, $[Na^+]_{tumor}$ increased 70-80% in both the untreated and BCNUnrsp groups (**Fig. c**). In contrast, $[Na^+]_{tumor}$ was relatively unchanged in BCNUrsp tumors and was significantly lower compared to the control and BCNUnrsp tumors after BCNU treatment. These ^{23}Na MRI data are in agreement with a previous spectroscopy study performed under the same experimental conditions (4). Other publications showed that $[Na^+]_{tumor}$ (1) and/or water ADC (1,5) mostly increased 3-7 days after chemotherapy. However, these studies differed from ours by the type of tumor, location, and/or type of chemotherapy.

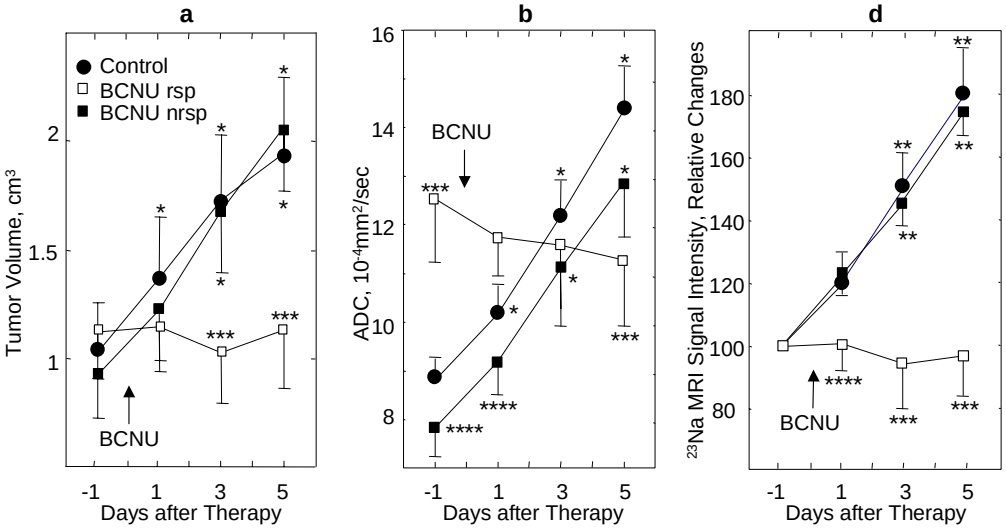

Figure. Effect of BCNU therapy (25 mg/kg, ip) on tumor volume, water ADC, and ^{23}Na signal intensity in sc-implanted 9L tumor. Significance: * $p \leq 0.05$ (vs. before treatment), ** (vs. day 1 after treatment), *** (vs. Control), **** (BCNUrsp vs. BCNUnrsp).

Conclusion

Our results suggest that the initial $[Na^+]_{tumor}$ and water ADC values may be useful as predictive parameters for tumor chemosensitivity. In this study, high levels of water ADC and $[Na^+]_{tumor}$ were a good prognosis for BCNU treatment. The increase in water ADC and $[Na^+]_{tumor}$ after chemotherapy does not appear to be a general phenomenon and may depend on many tumor characteristics, including location.

References

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