Real-Time Imaging of Emerging Resistance During Cancer Therapy

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Introduction:

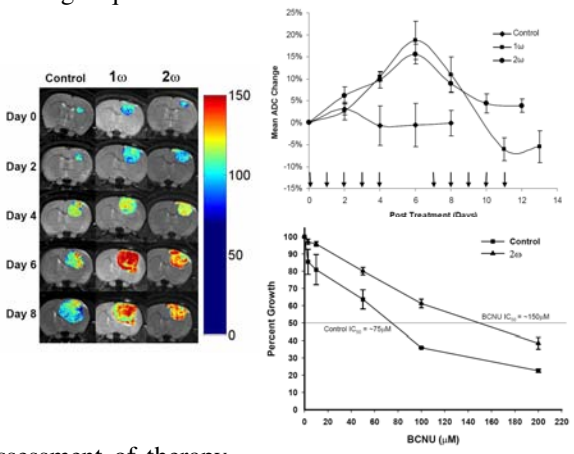
Though advances in therapeutic strategies have provided some success in managing brain neoplasms, the prognosis for highly aggressive tumors such as glioblastoma multiforme, is still poor with a median survival time of 9 months, and only 5 to 10% of patients surviving past 2 years [1]. Both resection and radiotherapy have proven to be effective methods in treating gliomas; however, adjuvant chemotherapy has yielded mixed results and is still a subject of controversy [2]. Even with optimal tumor response, there is a high rate of tumor recurrence of increased malignancy which is frequently refractory to further treatment. A number of studies suggest that the treatment-refractory nature of these recurrences, could result from previous chemotherapy [3, 4]. With tumors being such a dynamic entity, optimal therapeutic benefit presumably would require real-time management of the therapeutic regimen to account for these changes. This would require early, sensitive, and real-time assessment of therapeutic response. Diffusion MRI has emerged as a powerful tool that has garnered attention as a quantitative approach for assessment of tumor response to therapeutic intervention [5,6]. In this study, we employed the well-characterized orthotopic 9L glioma model to evaluate therapeutic response to different BCNU dosing regimens. We then demonstrate the ability of diffusion MRI to provide a quantitative real-time comparison of therapeutic response between one five day cycle of BCNU (1ω), and two similar cycles of BCNU therapy separated by a 2 day rest period (2ω). Our results demonstrated that not only did diffusion MRI provide an early prediction of therapeutic outcome, but it was also sensitive enough to immediately detect the loss of therapeutic response to BCNU. These results correlated with survival and with *ex vivo* determination of the emergence of drug-resistance in the treated tumors.

Methods:

Intracerebral 9L tumors were induced in Fischer 344 as previously described [7]. For treatment, BCNU was dissolved in absolute ethanol and diluted in saline at the time of treatment. Animals were subdivided into three groups. The 1ω group (n=5) received a total of 10mg/kg BCNU fractionated into daily 2mg/kg doses administered i.p. for 5 days. The 2ω group (n=17) received a total of 20mg/kg BCNU fractionated into daily 2mg/kg i.p. injections for 5 days, given 2 days of rest, and then 5 more daily 2mg/kg doses. Lastly, control animals with 9L tumor implants (n = 5) received injections of only vehicle (10% ethanol in saline) at volumes equivalent to treated groups for a complete 5-day cycle. T_2 images and diffusion maps were obtained on a 7 tesla Varian Unity Inova imaging system and images were acquired before treatment and at 2-day intervals thereafter. An isotropic, diffusion-weighted sequence was employed with two interleaved b-factors (b = 1148s/mm^2) and the following acquisition parameters: TR/TE = 3500/60ms, 128 x 128 matrix, and a 3cm FOV.

Results:

Our results demonstrate diffusion MRI predicted initial therapeutic response, but more importantly, also detected a loss of tumor response during ongoing therapy. Though the 2ω group received a much higher total dose of BCNU than the 1ω, the ADC values in the 2ω group decreased throughout the second cycle of therapy indicating a reduced cellular response to therapy. Representative tumors from the 2ω and vehicle control groups were excised and cell lines were established to analyze BCNU sensitivity. The SRB growth inhibition assay demonstrated that the treated tumors were more indeed more resistant to BCNU versus controls.



Discussion:

In summary, this report demonstrates that diffusion MRI can provide a rapid assessment of therapy-induced tumor response to fractionated therapeutic regimens as well as provide real-time detection of the emergence of chemoresistance. The findings of this study reveal the potential for diffusion MRI to play a major role in the preclinical development of therapeutic protocols using real time assessment of therapeutic effect. Moreover, this opens the opportunity for efficient optimization of treatment regimens as well as for applications in optimizing drug combinations, dosages, and schedules.

References

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