Modeled Temporal Responses of Tumor Volume and ADC to Anticancer Therapy

T. L. Chenevert[1], B. E. Layton[2], R. C. Welsh[3], S. Sharma[3], B. D. Ross[3]

[1]Radiology, University of Michigan, Ann Arbor, Michigan, United States, [2]Mechanical Engineering and Mechanics, Drexel University, Philadelphia, PA, United States, [3]Radiology, University of Michigan, Ann Arbor, MI, United States

Abstract

In this study we investigate the temporal relationship between changes in tumor volume and ADC following therapy using a compartmental model of tumor growth, therapeutic action, cell lysis and water clearance. The model was applied to fit tumor volume and ADC change measured on 9L glioma rats treated with BCNU, as well as treated brain tumor patients. Fitting these data yields estimates for the relative amplitude and duration of effective therapeutic action, necrosis production and clearance. In single-dose treatment of animals, the degree of therapeutic response increased with single dose amount. In protracted multi-dose schemes, however, the duration of effective therapeutic action did not scale with duration of therapy delivery suggesting development of therapy resistance. These observations are consistent with clinical results where the treatment schedule is protracted and increase in ADC following therapy is modest.

Introduction

Diffusion is being investigated as an early indicator of therapeutic response based on the premise that microscopic necrosis secondary to effective therapy is measurable as increase in ADC prior to mass shrinkage. This scenario has been demonstrated in numerous animal tumor studies [1-3], although its translation to human application has not been as consistent [4-7]. Previously, we introduced a simple theoretical model to explain these observations as a consequence of the relative timescales of tumor growth, therapeutic action, cell lysis, and clearance of excess extra cellular water [8]. In this work, we apply this model to estimate these relative time constants in treated animals and humans.

Materials and Methods

A model for the temporal dependencies of tumor volume and ADC following treatment was developed [8], but previously not applied to experimental data. Briefly, the compartment model includes viable tumor, non-viable but cellular tumor, and excess extra cellular water resultant from cellular lysis. The model incorporates shape functions to describe temporal conversion of viable to non-viable tumor by treatment (TVN), as well as conversion of non-viable tumor to extra cellular water (TLy). In this work, Rayleigh distribution functions were used. Tumor growth and excess water/debris clearance were modeled as exponentials. Input experimental data were tumor volume (sum of viable, non-viable, and excess water compartments) and ADC (volume-weighted sum of ADCs from each compartment). The model was applied to fit evolution of tumor volume and ADC in chemo-treated (BCNU) intracranial 9L glioma rats. Five animals were given a single "high dose" 26.6mg/kg BCNU injection (i.p.); two rats were given a single "low dose" 13.3mg/kg BCNU injection; and three rats received "multi dose" by daily injections of 2mg/kg BCNU for ten days over two weeks. Four untreated animals provided an estimate of tumor doubling time. Changes in tumor volume and ADC fit to the model using a chi-squares minimization routine. The model was also applied to volume and ADC time course data from patients to track even more gradual changes (i.e. over months).

Results

Figures 1, 2, and 3 illustrate rat data and model fits for change in tumor volume, ADC, and the conversion of viable to non-viable (TVN) tumor for representative single high dose, low dose, and multi dose animals respectively. Note the duration and area of TVN is approximately halved as the single chemotherapeutic dose is halved. For the multi dose animal, however, the amplitude of viable to non-viable conversion was reduced but its duration was not increased relative to the high dose rat despite the protracted treatment interval. Per model fits, the relative timescale of lysis (TLy) was much shorter than TVN and water clearance timescales for all rats. Applied to a brain tumor patient (anap. astrocytoma treated by chemo+XRT) shown in Figure 4, however, timescales for TVN, TLy, and clearance were more comparable.

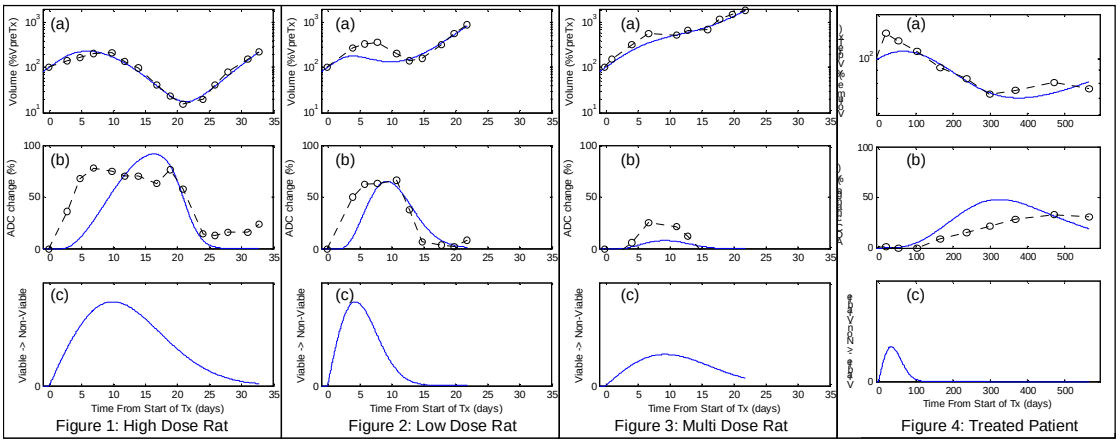

Figure 1: High Dose Rat | Figure 2: Low Dose Rat | Figure 3: Multi Dose Rat | Figure 4: Treated Patient

Figures1-4 (a) Change in tumor volume, and (b) ADC for treated rats (Figs 1-3) and one patient (Fig 4). Panels (c) illustrate fitted function for conversion of viable to non-viable tumor TVN.

Discussion / Conclusion

The model predicts that if the timescale of therapy-induced water production is reduced relative to water clearance, the magnitude of ADC increase is more pronounced and early relative to volume shrinkage. Conversely, protracted treatments and/or longer TLy lessen and delay ADC increase as is observed for brain tumor patients treated by conventional therapies. Animal data also suggests a resistance to therapy develops in multi-dose treatment administration.

References

1. Zhao M, Pipe JG, Bonnett J, Evelhoch JL. Br J Cancer(1996). 73:61–64.
2. Chenevert TL, McKeever PE, Ross BD. Clin Cancer Res(1997). 3:1457– 1466.
3. Galons JP, Altbach MI, Paine-Murrieta GD, Taylor CW, Gillies RJ. Neoplasia (1999). 1:113– 117.
4. Chenevert TL, Stegman LD, Taylor JM, et al. J Natl Cancer Inst (2000). 92:2029–2036.
5. Henson J., et.al. Neuro-Oncology (2000). 2(4) 269,.
6. Mardor Y., et. al. Cancer Research (2001) 61, 4971-4973.
7. Dzik-Jurasz A. et al. Lancet (2002). 360, 307-308.
8. Chenevert TL, Johnson TD, Schepkin VD, Ross BD. Proc. ISMRM (2003) 134.