Imaging the Timing of Cytotoxic and Anti-Angiogenic Therapy

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Target audience

This study is aimed at preclinical and clinical researchers interested in using MRI to better understand drug delivery to brain tumors and the consequences of blood-tumor barrier (BTB) normalization on delivery of chemotherapy.

Purpose

The blood-brain barrier (BBB) is a key factor in limiting delivery of anti-cancer drugs to brain tumors. The compromised neovasculature of the BTB is often the only means of systemically delivering cytotoxic agents. Anti-angiogenic therapies such as bevacizumab (BEV) have been shown to "normalize" brain tumor vasculature,[1] but the impact on chemotherapy delivery remains unclear.[2] The goal of this pilot study was to use MRI to elucidate vascular and interstitial fluid differences that correspond with the timing of temozolomide (TMZ) chemotherapy and BEV delivery.

Methods

Rats were inoculated in the right caudate nucleus with U87MG human glioma cells (12 µl, ~10^6 cells). When tumor volumes reached ~20-50mm^3, rats were randomized to: control (n = 1), BEV (45 mg/kg IV) followed by TMZ (40 mg/kg oral) (n = 2), and TMZ followed by BEV (n = 2). MRI was performed prior to treatment and 4 and 8 days after treatment using an 11.75 T magnet system. T_2W images were acquired for detection of edema. DCE-MRI was accomplished with a fast-gradient-echo sequence. MRI sequence parameters were used from our previous work.[1] K^{trans} was calculated by non-linear squared fitting to the T_1 measurements using a two-compartment model; animal-specific arterial input functions were implemented.

Results

The timing/sequencing of BEV and TMZ delivery could be important to the overall anti-tumor efficacy (Fig. 1). When BEV was delivered first, permeability (average K^{trans}) was decreased 65% before the delivery of TMZ (Fig. 1A); after TMZ was delivered, average K^{trans} increased 23%, which could represent some reversal of the BTB normalization. When TMZ was delivered first, average K^{trans} was increased 37% before the delivery of BEV (Fig. 1B) corresponding with edema as shown in the T_2-weighted image after this treatment. The subsequent delivery of BEV resulted in a 60% decrease of average K^{trans}. Average K^{trans} for control increased over the course of the study (Fig. 1C).

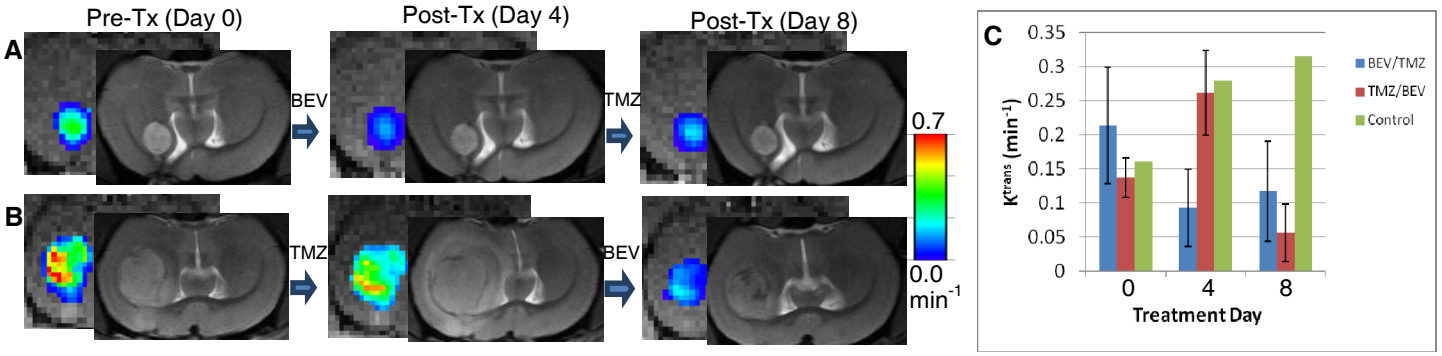

Fig. 1. Effect of timing on BEV and TMZ in glioma. A. Permeability in glioma treated with BEV followed by TMZ. In the background, K^{trans} maps that show the spatial heterogeneity of permeability; in the foreground, corresponding T_2W images in foreground at pre-treatment (day 0), post-first treatment (day 4), and post-second treatment (day 8) of treatment regimen. B. Permeability in glioma treated with TMZ followed by BEV. T_2W images after TMZ shows edema. C. Average K^{trans} comparison for all animals and treatment groups.

Discussion

This pilot study raises two important points: (1) When TMZ is given after BEV there is no apparent edema, which may indicate reduced delivery of TMZ; (2) When TMZ is given prior to BEV there appears to be more anti-tumor effect as shown by the hypointense regions (possible necrosis) within the tumor of Fig. 1B (day 8), while this is not observed in Fig. 1A (day 8).

Conclusion

The pilot study shows promise that it may be more effective to deliver chemotherapy before tumor vascular normalization and warrants further study. Histology can provide a path to quantify efficacy. EVAC-imaging[3] or proton density quantification may be a better way than T_2W images to quantify changes in the interstitial fluid environment.

References

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