Rat liver tumor treated with a vascular disrupting agent combined with an antiangiogenic: enhanced antitumor efficacy evaluated by MRI

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Background and Purpose
A key problem in solid tumor therapy is tumor regrowth from a residual viable rim after treatment with a vascular disrupting agent (VDA). As a potential solution, we studied a combined treatment of a VDA and antiangiogenic.

Methods
This study was approved by the institutional ethical committee for the use and care of laboratory animals. We evaluated the results with multiparametric MRI. Rats with implanted liver tumors were randomized into four treatment groups: 1) Zd6126 (Zd); 2) Thalidomide (Tha); 3) Zd in combination with Tha (ZdTha); and 4) controls. MRIs were performed and quantified before and after treatment. Circulating endothelial progenitor cells (EPCs) and plasma stromal cell-derived factor-1α (SDF-1α) were monitored. Tumor apoptosis, necrosis, and microvessels were verified by histopathology.

Results
A single use of Zd or Tha did not significantly delay tumor growth. The combined ZdTha showed enhanced antitumor efficacy due to synergistic effects; it induced a cumulative tumor apoptosis or necrosis, which resulted in significant delay in tumor growth (Fig. 1) and reduction in the viable tumor rim; it also reduced tumor vessel permeability; and it improved tumor hemodynamic indexes, most likely via a transient normalization of tumor vasculature induced by Tha. A stepwise linear regression analysis showed that the apparent diffusion coefficient was an independent predictor of tumor volume changes (r=-0.652, P=0.030).

Conclusions
ZdTha showed improved therapeutic efficacy in solid tumors compared to either agent alone. The therapeutic effects were successfully tracked in vivo with multiparametric MRI.

References