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.

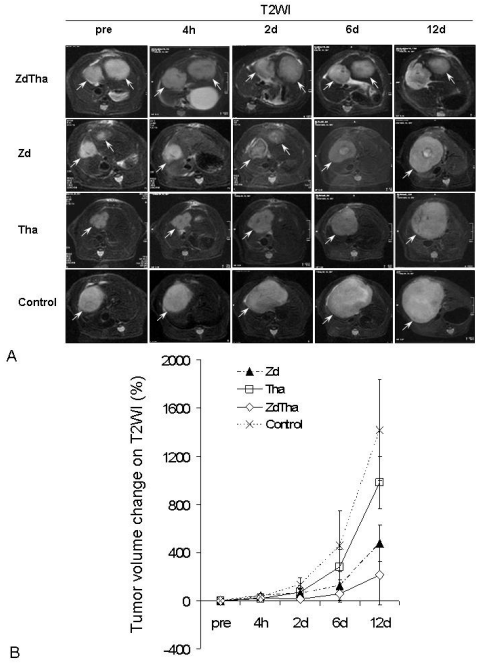

Fig. 1

Fig. 1 Among the four treatment groups, ZdTha induced the largest reductions in tumor volumes. (A) Representative axial images of liver tumors on T2WIs. The tumor (arrow) with the most significantly delayed growth was in the combined therapy group (ZdTha). (B) Mean tumor volume changes after treatment compared to pretreatment measured on T2W images in the four treatment groups (P<0.05 for ZdTha vs all groups at 2d and 6d; P<0.05 for ZdTha vs control and Tha at 12d).

Fig. 2 Dynamic change of the tumor ADC values. ZdTha treatment showed the highest increase of ADC since 2d after treatment. The ADC change at 12 d was significantly negatively correlated with the tumor volume change compared to pretreatment values, and was the only independent predictor of tumor volume changes (r=-0.652, P=0.030).

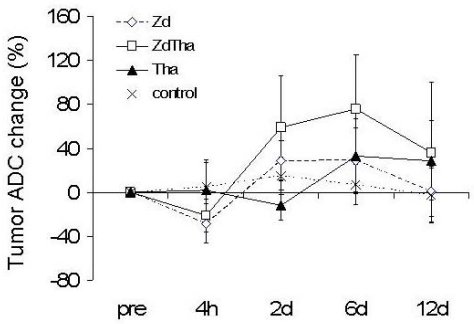

Fig.2

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.

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 growth (**Fig.2**). We found no significant increases in Zd-induced circulating EPCs or plasma SDF-1α.

References

1. Tozer, G. M, et al. Nat Rev Cancer, 2005;5*:* 423-35.

2. Siemann, D. W, et al. Int J Radiat Oncol Biol Phys 2004;60*:* 1233-40.

3. Kanthou, C, et al. Int J Exp Pathol, 2009;90*:* 284-94.

4. Padhani, A. R, et al. Radiology, 2010;256: 348-64

5. Chen, F., et al. Radiology, 2006;239: 554-62.