Dynamic Contrast-Enhanced Magnetic Resonance Imaging enables personalized anti-EMMPRIN therapy for pancreatic cancer

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Purpose: To demonstrate how dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) might be used to select pancreatic cancer patients favorably responding to combination therapy with anti-EMMPRIN antibody and chemotherapeutic agents.

Materials and Methods: A total of 13 groups of SCID mice (n=5-6/group) bearing orthotopic MIA PaCa-2 tumors were employed. Group 1 was used to examine the change of tumor vascularity over tumor size; DCE-MRI was applied during four consecutive days, and tumor volume, K^{trans}, k_{ep}, and the concentration of MR contrast (prohance) at 20 minutes after injection (CC_{20min}; interpreted as the delivery efficiency of a non-targeting small-molecule chemotherapeutic agent like gemcitabine) were quantified. The correlation between tumor volume and the vascular parameters (K^{trans}, k_{ep}, CC_{20min}) were determined, and thereafter the correlation between K^{trans} and CC_{20min} was retrieved. Tumors were classified into hyper, normal, and hypovascular tumors, assuming that normal vascular tumors have CC_{20min} higher than 80% of the maximum value. Groups 2-13 were used to evaluate the efficacy of combination therapy with anti-EMMPRIN antibody and small-molecule chemotherapeutic agents; therapy started when tumors of groups 2-5 were hypervascular, and tumors of groups 6-13 were hypovascular. Group 2 (or group 6) was untreated (served as control), and groups 3-5 (or groups 7-9) were treated with gemcitabine, anti-EMMPRIN antibody, and combination, respectively, for 2 weeks. The same dose schedule used for groups 6-9 was applied to treat groups 10-13, respectively, but β-lapachone was added to the therapy regimen of each group. FDG-PET/CT imaging was applied weekly for all animals in groups 2-13, and tumor volume and tumor SUV_{mean} were quantified.

Results: Mean K^{trans} and k_{ep} values in the tumor region were linearly proportional to the tumor-volume change, but CC_{20min} was maximized when tumor volume was ~130 mm^3 (or when K^{trans} value was ~0.05 min^{-1}) and then declined (**Fig 1**). The K^{trans} range of normal vascular tumors was determined to be 0.045~0.065 min^{-1} (**Fig 1**). **Figure 2** shows the representative MR contrast (prohance) concentration maps acquired from DCE-MR images of hyper, normal, and hypovascular orthotopic pancreatic tumors. **Figure 3A** shows the synergy between anti-EMMPRIN antibody and gemcitabine when tumors were hypervascular, but **Figure 3B** shows antagonistic effect between them in hypovascular tumors. The antagonistic effect appeared more obvious in triple combination therapy with gemcitabine, anti-EMMPRIN antibody, and β-lapachone in hypovascular tumor (**Fig 3C**), although additive effect was observed between gemcitabine and β-lapachone (**Fig 3D**). Tumor volume change was significantly correlated with tumor SUV_{mean} change either in the hypervascular tumor model (p=0.002) or hypovascular tumor model (p=0.0025).

Discussion: Synergy between anti-EMMPRIN antibody and gemcitabine was observed in a hypervascular pancreatic tumor model, whereas antagonistic effect was shown in a hypovascular tumor model. For hypervascular tumors, the antiangiogenic effect of anti-EMMPRIN antibody may induce the normalization of tumor microvasculature, reducing interstitial pressure and thereby improving the delivery of gemcitabine (or other small-molecule chemotherapeutic agents). In contrast, for hypovascular tumors, the antiangiogenic effect reduces the tumor vasculature excessively, decreasing the tumor delivery of small-molecule chemotherapeutic agents, leading to antagonistic effect. Therefore, it would be essential to measure tumor vascularity prior to therapy initiation to decide whether anti-EMMPRIN antibody will need to be used together with chemotherapy (that is, personalized anti-EMMPRIN therapy) based on DCE-MRI.

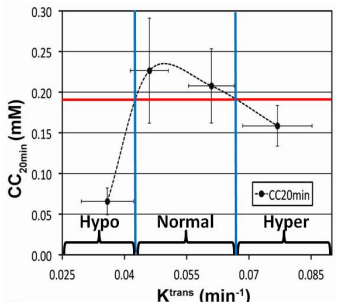

Figure 1. Drug-delivery efficiency (CC_{20min}) over tumor K^{trans} value. Red line represents 80% level of the maximum CC_{20min} value.

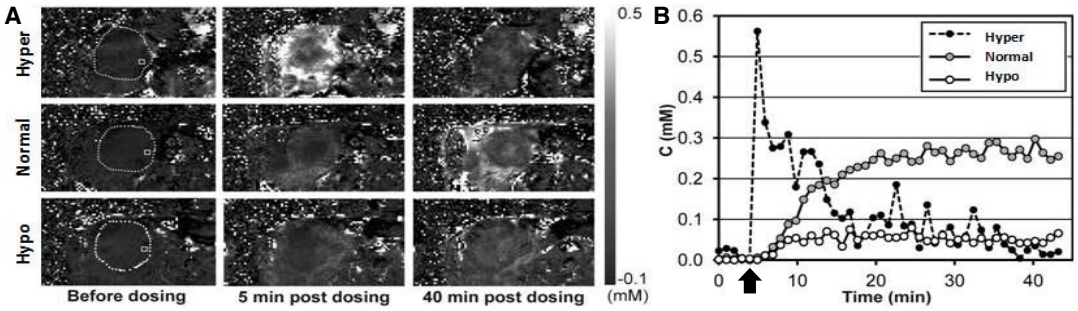

Figure 2. (A) Representative MR contrast (prohance) concentration maps acquired from DCE-MR images of hyper, normal, and hypovascular orthotopic pancreatic tumors at 0 (baseline), 5, and 40 minutes after contrast injection. (B) Contrast-enhancement curves averaged in the ROI indicated with the white square shown in Fig. 2A, while the time point of prohance injection is indicated with a black arrow.

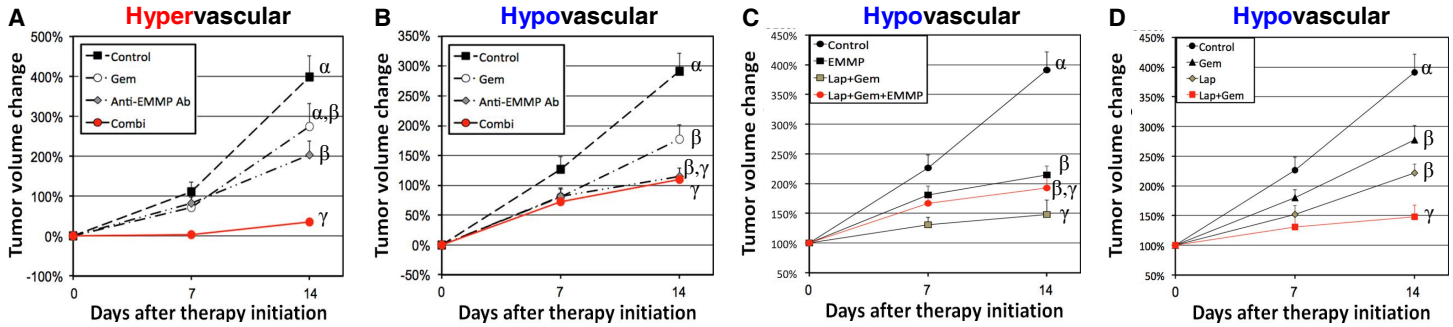

Figure 3. (A,B) Tumor volume changes of four groups untreated or treated with gem, EMMP, and gem+EMMP, when tumors were (A) hypervascular or (B) hypovascular. (C) Tumor volume changes of four groups untreated or treated with EMMP, lap+gem, and lap+gem+EMMP, respectively, when tumors were hypovascular. (D) Tumor volume changes of four groups untreated or treated with Gem, lap, and lap+gem, respectively, when tumors were hypovascular. Statistical differences among groups are represented with different Greek letters (Lap: β-lapachone; EMMP: anti-EMMPRIN antibody; Gem: gemcitabine).