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

Hyunki Kim1, Christopher Rigell1, Guihua Zhai1, Kyle Lee1, Sharon Samuel1, Amber Martin1, Timothy Beasley1, Long Shan Li2, David Boothman1, and Kurt Zinn1

1University of Alabama at Birmingham, Birmingham, AL, United States, 2Radiation Oncology, UT Southwestern Medical Center, Dallas, TX, United States

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 chemotherapy 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, Ktrans, kep, and the concentration of MR contrast (prohance) at 20 minutes after injection (CC20min) were determined. The correlation between tumor volume change and the vascular parameters (Ktrans, kep, CC20min) were determined, and thereafter the correlation between Ktrans and CC20min was retrieved. Tumors were classified into hyper, normal, and hypovascular tumors, assuming that normal vascular tumors have CC20min 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 SUVmean were quantified.

Results: Mean Ktrans and kep values in the tumor region were linearly proportional to the tumor-volume change, but CC20min was maximized when tumor volume was ~130 mm3 (or when Ktrans value was ~0.05 min-1) and then declined (Fig 1). The Ktrans 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, and 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 tumors (Fig 3C), although additive effect was observed between gemcitabine and β-lapachone (Fig 3D). Tumor volume change was significantly correlated with tumor SUVmean 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 (CC20min) over tumor Ktrans value. Red line represents 80% level of the maximum CC20min 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).