Dynamic Contrast Enhanced Magnetic Resonance Imaging Evaluates Therapeutic Mechanism of nab-Paclitaxel in Pancreatic Cancer Patient Derived Xenograft Mouse Models.

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Purpose: To identify the therapeutic mechanism of *nab*-paclitaxel in pancreatic cancer by monitoring tumor microperfusion using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) in pancreatic cancer patient derived xenograft (PDX) mouse models.

Materials and Methods: Pancreatic cancer patient derived xenograft (PDX) tissues labeled Panc039 and Panc198 were used. Four groups (n=5/group) of mice bearing Panc039 tumors or Panc198 tumors were untreated (served as control) or treated with gemcitabine (100 mg/kg BW, *i.p.*, twice per week), *nab*-paclitaxel (30 mg/kg BW, *i.v.*, for 5 consecutive days), and gemcitabine plus *nab*-paclitaxel for 3 weeks, respectively. MRI was applied on days 0 and 21 with a 9.4T system (Bruker BioSpin Corp., Billerica, MA). Anatomical MRI to measure tumor volume was performed using RARE T2-weighted turbo spin-echo sequence with the following acquisition parameters: TR/TE=2000/34 ms, 128x128 matrix, and a 30x30-mm FOV. Continuous 1-mm thick slices were used to cover the entire tumor region. T1 map was acquired with a gradient-echo multiflip-angle approach with the following parameters: TR/TE=115/3 ms, 128x128 matrix, a 30x30-mm FOV, NEX=4, and seven flip angles of 10, 20, 30, 40, 50, 60, and 70°. A total of five to seven 1-mm thick slices were acquired to cover tumor regions of interest in an interlaced mode. DCE-MRI employed the same acquisition parameters as those above but with the fixed flip angle of 30°. Five baseline images were acquired before gadoteridol injection, and then 40 images were acquired after gadoteridol injection (0.2 mmol/kg BW) over a period of 15 seconds with a total injection volume of 0.15 ml. The reference region (RR) model was employed to calculate K^{trans} values. On day 21, all tumors were collected and stained using Masson's Trichrome Stain Kit, and tumor stroma density was quantitated. We used two additional groups (n=8/group) bearing Panc039 or Panc198 tumors, respectively, to assess the tumor delivery of *nab*-paclitaxel. IR800 labeled *nab*-paclitaxel was injected to all animals, and tumors were collected at 24 hours thereafter.

Results: Panc039 and Panc198 tumor volumes decreased 39±12% and 67±9%, respectively, after *nab*-paclitaxel treatment for 3 weeks, while gemcitabine also presented a comparable anti-tumor effect (58±7% and 65±9% reduction in Panc039 and Panc198, respectively) (Figs. 1C and 1E). An additive effect was observed when *nab*-paclitaxel was used in combination with gemcitabine (84±3% and 82±5% reduction in Panc039 and Panc198, respectively). Of interest, in the Panc039 model, mean K^{trans} value in gemcitabine treated tumors increased 269±71%, significantly different from the K^{trans} changes with *nab*-paclitaxel treatment (p=0.017) and no treatment (p=0.003) (Fig. 1D). Mean K^{trans} value in tumors treated with gemcitabine plus *nab*-paclitaxel also increased to a similar magnitude (309±50%). In the Panc198 model, gemcitabine therapy increased tumor K^{trans} value 30±17%, which was significantly different from the K^{trans} change in untreated tumors (p=0.014), but in *nab*-paclitaxel treated tumors K^{trans} was unchanged during the same time period (0±8%). Collagen fiber density in tumors treated with *nab*-paclitaxel was significantly higher than that in untreated tumors in both Panc039 (p=0.004) and Panc198 (p=0.042) models. Also, IR800 labeled *nab*-paclitaxel was markedly distributed in tumor stroma.

Discussion: It has been hypothesized that *nab*-paclitaxel may deplete tumor stroma, reducing the solid stress of tumors, which leads to relief for the compression on tumor vessels, the increased blood perfusion and in turn the improved drug delivery. But our findings indicate that nab-paclitaxel does not deplete tumor stroma or increase tumor microvascular perfusion. Therefore the significant clinical benefits of *nab*-paclitaxel may result from its efficient delivery into tumors in pancreatic cancer.

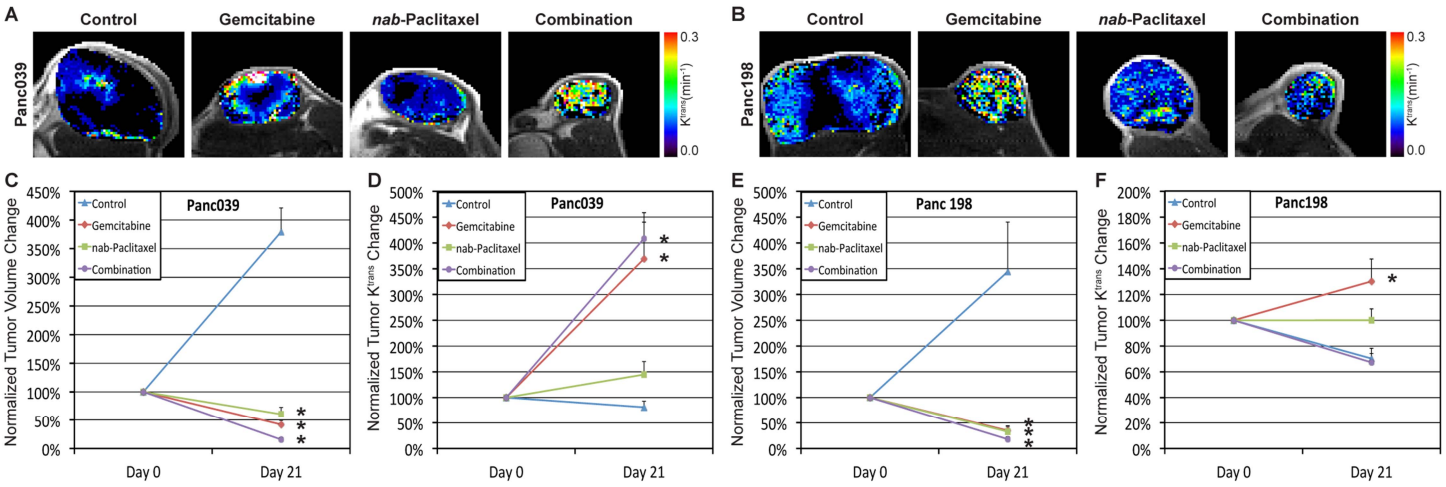

Figure 1. Changes of tumor volume and K^{trans} value. (A) Panc039 or (B) Panc198 tumor xenografts untreated (control) or treated with gemcitabine, *nab*-paclitaxel, or the combination for 3 weeks. K^{trans} values in tumor regions are shown in the color scale. (C, E) Mean tumor volumes of (C) Panc039 and (E) Panc198 before therapy (Day 0) and at 3 weeks after therapy initiation. (D, F) Mean tumor K^{trans} values of (D) Panc039 and (F) Panc198 before therapy (Day 0) and at 3 weeks after therapy initiation. Asterisks represent statistical difference from untreated control group.