Evaluation of combination treatment benefits of nab-paclitaxel in experimental pancreatic cancer.

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**Abstract:**

**Background:** Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive human cancers and is characterized by early tissue invasion, metastasis and high resistance to systemic therapies. Gemcitabine, a standard cytotoxic therapy for pancreatic cancer, has shown limited clinical benefits. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel), an approved treatment for breast cancer, has shown efficacy as mono- and combination therapy in multiple tumor types including pancreatic, lung and ovarian cancer. We evaluated combination treatment benefits of nab-paclitaxel with gemcitabine in experimental pancreatic cancer.

**Methods:** In vitro cell proliferation was evaluated by WST-1 assay in human PDAC cells. Animal survival studies were performed in murine xenografts.

**Results:** Nab-paclitaxel inhibited in vitro proliferation of PDAC cell lines with IC50 levels of 7.6 mM, 208 nM, 519 nM and 526 nM for AsPC-1, BxPC-3, MIA PaCa-2 and Panc-1 cells. Nab-paclitaxel combination with gemcitabine had significant additive effect on inhibition of PDAC cell proliferation; 72-hour incubation demonstrated that nab-paclitaxel addition caused a 2.5, 2.5, 8.9 and 2.2-fold decrease in IC50 of gemcitabine in AsPC-1, BxPC-3, MIA PaCa-2 and Panc-1 cells, respectively. In an intraperitoneal murine xenograft model, 2-week therapy demonstrated that compared to controls (median survival: 23 days), animal survival increased after gemcitabine (27 days, p=0.05) and nab-paclitaxel monotherapy (35 days, p=0.0005). In a separate 3-week therapy experiment, animal survival was significantly longer in the nab-paclitaxel treated group (41 days, p<0.002 versus control and Gem) compared with gemcitabine (32 days, p=0.005 versus control), docetaxel (32 days, p=0.005) and controls (20 days). Animal survival in nab-paclitaxel / gemcitabine and docetaxel / gemcitabine sequential treatment group was 43 and 40 days, respectively.

**Conclusions:** Nab-paclitaxel has significant antitumor activity as a single agent in experimental pancreatic cancer and can also enhance gemcitabine effects in combination. These findings provide a strong rationale for testing nab-paclitaxel in patients with pancreatic cancer.
Gemcitabine (G) and nab-paclitaxel (nab-P) in patients with refractory advanced pancreatic cancer (PC).

**Background:** There is no standard chemotherapy regimen for PC patients who have progressed on G and fluoropyrimidine-based therapy. Single agent nab-P had limited activity on a second-line phase II trial in PC. Synergistic preclinical studies with G and taxanes have been reported. Nab-P targets stromal cells and leads to improved delivery of chemotherapy to PC cells. The combination of G + nab-P might be an effective approach in pretreated PC.

**Methods:** A retrospective analysis of advanced refractory PC patients treated from Sep 2010 to Aug 2011 with the combination of G + nab-P was performed at the Sylvester Comprehensive Cancer Center. Patients received G 1000mg/m² and nab-P 100mg/m² on D1, 8 and 15 of a 28 day cycle. Treatment response was assessed by review of imaging studies using the RECIST criteria, CA19-9 response and symptomatic improvement. The progression-free survival (PFS) and overall survival (OS) were calculated from time of commencement of G + nab-P until documented progression or death respectively.

**Results:** 10 patients were treated with G + nab-P; 60%, 30% and 10% of patients had received 3, 2 and 1 prior chemotherapy regimen. 90% and 80% received prior G or fluoropyrimidine-based regimen respectively. Therapy was discontinued in one patient following only one dose of G + nab-P (Cycle 1, day 1) due to grade 2 thrombocytopenia. The remaining 9 patients received a median of 4 cycles. Two (22.2%) patients had confirmed PR, 3 (33.3%) patients had confirmed stable disease while 4 (44.4%) patients progressed on therapy. The median PFS was 13.7 weeks. The median PFS was 20 weeks in patients with PR or SD and 9.9 weeks in patients with PD. Recurrent malignant ascitis resolved in a patient with peritoneal carcinomatosis. Treatment was well tolerated; grade 3-4 hematoologic toxicity included anemia, thrombocytopenia and neutropenia in 2, 1 and 2 patients respectively. 70% of patients required G-CSF support. Non hematologic Grade 3-4 toxicities included fatigue, peripheral neuropathy; nausea and vomiting in 3, 2 and 1 patient respectively.

**Conclusions:** G + nab-P resulted in clinical benefit in half of this group of advanced PC patients who had previously progressed on G and fluoropyrimidine-based regimens.