Anticancer effect of PBI-0110 in combination with gemcitabine in intradradr and orthotopic pancreatic cancer

Lyne Gagnon, Lilianne Geerts, François Sarra-Bournet, Liette Gervais, Brigitte Grouix and Mouna Lagraoui
ProMetic BioSciences Inc., Laval, Québec, Canada HV 5B7

ABSTRACT
Carcinoma of the exocrine pancreas has a particularly poor prognosis. Five-year survival is only 3-5%. Radical pancreaticoduodenectomy is the mainstay of treatment for minimal disease, is currently the only chance of cure. Although chemotherapy has led to improvement in survival in patients with locally advanced disease, the overall effect is small. Also, surgery or radiotherapy of locally advanced unresectable pancreatic cancer does not lead to significantly prolonged survival. Therefore, novel therapeutic strategies are required. PBI-0110 is a well-defined, low active molecule that has been shown to localize specifically in the extracellular matrix (ECM) and to inhibit tumor growth. PBI-0110 has been shown to induce cell death in vitro cytoxicity towards Panc02 cell line and to suppress tumor growth in the intradradr and orthotopic Panc02 tumor model. The antitumor efficacy of oral administration of PBI-0110 (100 mg/kg) was studied in combination with the standard therapy, gemcitabine (50 mg/kg), in intradradr pancreatic Panc02 cancer. Mice were treated every day with oral administration of vehicle (negative control), or PBI-0110 (200 mg/kg) and with intraperitoneal injection of gemcitabine (50 mg/kg) once a week. Tumors were evaluable, in general, 3-5 days post-inoculation. Gemcitabine induces a significant inhibition (p < 0.05) of tumor growth from day 23 to 44 with a T/C from 60% to 58%. Furthermore, PBI-0110 induced a significant inhibition of the tumor growth in a dose dependent manner. A significant tumor growth inhibition was observed from day 23 to 37 (p < 0.05) when PBI-0110 was used at a dose of 400 mg/kg. A T/C < 40% was observed from day 23 to 37 compared to control and at day 37, 31 and 29 to 39 when compared to gemcitabine alone. The effect of PBI-0110 in combination with gemcitabine was also studied in an orthotopic model of pancreatic cancer. After orthotopic injection of Panc02 cells into the pancreas, all animals developed tumors that were palpable. Mice developed ascites with abdominal metastases, mostly observed in liver, bile duct, spleen, diaphragm and mesentery. Mice treated with gemcitabine or a combination of gemcitabine and PBI-0110 showed prolonged survival compared to mice that received vehicle (control). Median survival was 71 days for gemcitabine-treated mice compared with 48 days in control mice. Mice treated with the combination of gemcitabine and PBI-0110 lived 88 days. These results suggest that PBI-0110 has the potential to inhibit the growth of pancreatic cancer.

METHODS AND RESULTS

Antitumor efficacy of PBI-0110 in the Panc02 pancreatic cancer mouse model

Gemcitabine (Gemc) 100 mg/kg was injected intraperitoneally every week beginning at day 0. Gemcitabine (Gemc) 100 mg/kg and PBI-0110 (100 mg/kg) were administered intraperitoneally every week beginning at day 0. The effect of oral administration of PBI-0110 and gemcitabine on survival of mice was evaluated by Kaplan-Meier survival analysis. Day 0 was set as the time point at which mice developed a palpable tumor, which is the time at which the animals were euthanized and examined. All injection of Panc02 cells, all animals developed tumors that were palpable. Mice developed ascites with abdominal metastases. Metastasis were mostly observed in liver, bile duct, spleen, diaphragm and mesentery. These results suggest that PBI-0110 can be used as adjunct to gemcitabine in pancreatic cancer.

CONCLUSION
PBI-0110 is a low molecular synthetic orally active compound. PBI-0110 displays significant antitumor activity against xenograft Panc02 tumors in mice. PBI-0110 demonstrates synergistic antitumor activity in combination with a sub-therapeutic dose of gemcitabine. These results suggest that PBI-0110 can be used as adjunct to gemcitabine in pancreatic cancer.