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

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Abstract

Carcinoma of the exocrine pancreas has a particularly poor prognosis. Five-year survival is only 3-5%. Radical pancreaticoduodenectomy, especially 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 molecular weight orally active molecule. PBI-0110 has been shown to induce *in vitro* cell cytotoxicity towards Panc02 cell line and to suppress tumor growth in the intradermal 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 (ip, 50 mg/kg), in intradermal pancreatic Panc02 cancer. Mice were treated every day with oral administration of vehicle (negative control), or PBI-0110 and with intraperitoneal injection of gemcitabine (50 mg/kg) once a week. Tumors were palpable, in general, 3-5 days post-inoculation. Gemcitabine induced a significant inhibition ($p < 0.05$) of tumor growth from day 27 to 34 with a T/C from 55% to 78%. PBI-0110 induced a significant inhibition ($p < 0.05$) of tumor growth from day 23 to 44 with a T/C from 26% 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 at day 23 and 25. The combination regimen (gemcitabine + PBI-0110, 100 mg/kg) induced a significant ($p < 0.05$) inhibition of the tumor growth and a T/C < 40% from day 23 to 37 when compared to control and at day 23, 25 and 30 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 mesenteries. 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 have a median survival of 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

Syngeneic Panc02 is a pancreatic adenocarcinoma tumor cell line obtained from NCI (0507232). Panc02 cells are positive for Ki-Ras, p53, HerNEU and CDK. Panc02 cells were grown in RPMI-1640 containing 10% fetal bovine serum. At day 0, 50 µl of 7.5 x 10^5 viable Panc02 cells were injected intradermally into 6 to 8-week old C57BL/6 mice. The animals were then monitored by manual palpation for evidence of tumor growth which, in general, took 3-5 days post-inoculation. On day 21, mice were treated daily with an oral administration of vehicle (negative control), PBI-0110 or with an intraperitoneal injection of gemcitabine (positive control) at day 21, 28, 35 and 42. The animals were sacrificed between day 36 to 50.

Figure 1 represents the antitumor efficacy of PBI-0110 (oral, 100 mg/kg) and gemcitabine (ip, 50 mg/kg) in pancreatic Panc02 cancer.

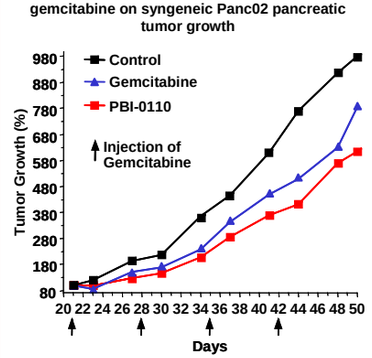

Figure 1

- Gemcitabine induces a significant inhibition ($p < 0.05$) of tumor growth from day 27 to 34 with a growth inhibition from 55 to 78%.
- PBI-0110 induces a significant inhibition ($p < 0.05$) of tumor growth from day 23 to 44 with a growth inhibition from 26 to 58%.

Figure 2 shows the antitumor efficacy of oral administration of PBI-0110 (100, 200 and 400 mg/kg), gemcitabine (50 mg/kg) and a combination of gemcitabine (ip) with PBI-0110 (400 mg/kg) in pancreatic Panc02 cancer. Animals of most treatment groups were sacrificed at day 37. However, mice treated with gemcitabine and with the combination therapy were not sacrificed until day 42 so that tumor outgrowth could be assessed after treatment. In both of the latter groups, the tumor continued to grow after the treatments were stopped.

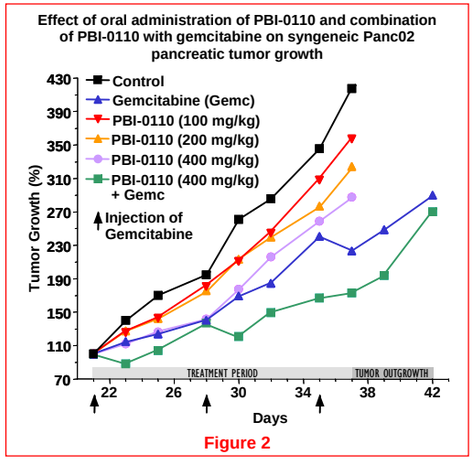

Figure 2

- Gemcitabine induces a significant inhibition ($p < 0.05$) of tumor growth from day 23 to 37. A T/C < 40% was observed at day 23, 25 and 37.
- PBI-0110 induces a significant inhibition of the tumor growth in a dose dependent manner. A significant inhibition ($p < 0.05$) of tumor growth, compared to control, was observed from day 23 to 37 when used at a concentration of 400 mg/kg of PBI-0110. A T/C < 40% was observed at day 23 and 25.
- The combination regimen (gemcitabine + PBI-0110, 100 mg/kg) induces a significant inhibition ($p < 0.05$) of tumor growth and a T/C < 40% from day 23 to 37.
- The inhibition of tumor growth induced by the combination therapy was significant ($p < 0.05$) compared to gemcitabine alone at day 23, 25 and 30 to 39.

Anti-tumor efficacy of PBI-0110 in the Panc02 orthotopic pancreatic cancer mouse model

On day 0, 6- to 8-week old C57BL/6 mice were inoculated with 50 µl solution containing 1 x 10^6 viable Panc02 cells directly into the pancreas to produce orthotopic tumors. Mice were then 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 (day 1, 8, 15, etc). The experimental endpoint (death) was defined as the time point at which mice developed a distended abdomen due to ascites or exhibited moribund behavior, at which time the animals were euthanized and examined.

After injection with Panc02 cells, all animals developed tumors that were palpable. Mice developed ascites with abdominal metastases. Metastases were mostly observed in liver, bile duct, spleen, diaphragm and mesenteries.

Figure 3 represents the survival of mice after oral administration of PBI-0110 (200 mg/kg) in combination with gemcitabine (ip, 50 mg/kg) compared to gemcitabine alone in the orthotopic pancreatic Panc02 cancer model.

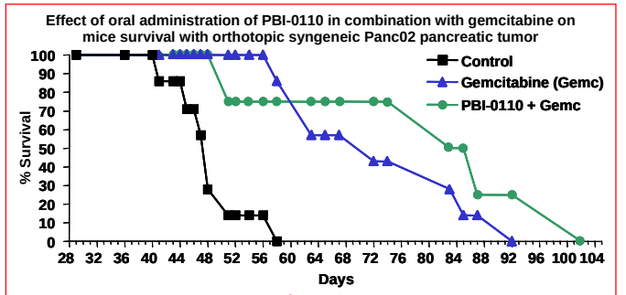

Figure 3

- Mice treated with gemcitabine and a combination of gemcitabine and PBI-0110 demonstrate prolonged survival compared to the control group (vehicle).
- Median survival is 71 days for gemcitabine-treated mice compared with 48 days in the control group.
- Median survival is 88 days for mice treated with the combination of gemcitabine and PBI-0110.

Table 1 depicts mouse survival after treatment with gemcitabine and gemcitabine plus PBI-0110 shown in Figure 3.

Table 1: Effect of oral administration of PBI-0110 in combination with gemcitabine on survival of mice

DAYS	GROUPS	% SURVIVAL
58	Control	0
	Gemcitabine	86
	Gemcitabine + PBI-0110	75
72	Control	0
	Gemcitabine	42
	Gemcitabine + PBI-0110	75
83	Control	0
	Gemcitabine	28
	Gemcitabine + PBI-0110	50
87	Control	0
	Gemcitabine	14
	Gemcitabine + PBI-0110	25
92	Control	0
	Gemcitabine	0
	Gemcitabine + PBI-0110	25

- At day 58, there are no survivors in control group.
- At day 58, 86% of the mice treated with gemcitabine survived.
- At day 58, 75% of mice treated with gemcitabine + PBI-0110 survived.
- Between day 72 and day 87, treatment with the combination (gemcitabine + PBI-0110) extended survival by almost two fold when compared to the gemcitabine treated group.
- At day 92, no mice survived in the gemcitabine-treated group.
- At day 92, 25% of the mice survived in the gemcitabine + PBI-0110-treated group.
- At day 102, the remaining mouse treated with the drug combination died.

Conclusion

- PBI-0110 is a low molecular synthetic orally active compound.
- PBI-0110 displays significant antitumor activity against pancreatic cancer.
- PBI-0110 demonstrates synergistic antitumor activity in combination with a sub-therapeutic dose of gemcitabine.
- PBI-0110 in combination with gemcitabine increases survival of mice in the Panc02 orthotopic pancreatic model in mouse.
- PBI-0110 does not belong to the class of cytotoxic drugs.

These results suggest that PBI-0110 can be used as adjunct to gemcitabine in pancreatic cancer.