Published in final edited form as:

Invest New Drugs. 2012 February ; 30(1): 382–386. doi:10.1007/s10637-010-9526-z.

Gemcitabine plus sorafenib in patients with advanced pancreatic cancer: a phase II trial of the University of Chicago Phase II Consortium

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Summary

Background—Sorafenib, an inhibitor of B-raf, VEGFR2, and PDGFR- β , has activity against pancreatic cancer in preclinical models. In a phase I trial of gemcitabine plus sorafenib, 57% of pancreatic cancer patients achieved stable disease.

Patients and methods—We conducted a multi-center phase II trial of sorafenib plus gemcitabine in chemo-naïve patients with histologically confirmed, advanced pancreatic cancer. Patients received sorafenib 400 mg twice daily and gemcitabine 1,000 mg/m² on days 1, 8 and 15 of a 28 day cycle.

Results—Seventeen patients enrolled at 4 centers; 13 were evaluable for response. There were no objective responses; 18% had stable disease. Median overall survival was 4.0 months (95% CI: 3.4, 5.9); median progression-free survival was 3.2 months (95% CI: 1.6, 3.6). Grade 3/4 toxicities included thrombosis in 18% of patients, dehydration or hand-foot syndrome in 12%, and hypertension or gastrointestinal bleeding in 6%.

Conclusion—Gemcitabine plus sorafenib is inactive in advanced pancreatic cancer.

Keywords

Pancreatic cancer; Phase II trial; Gemcitabine; Sorafenib

Introduction

Pancreatic cancer has the worst survival of any solid tumor, with a five-year survival rate of less than 5% [1]. Because the initial symptoms are generally non-specific, most patients present after their cancer has already metastasized or has become too locally invasive to permit resection. Their survival is brief, measured in months.

Since 1996, the cornerstone of chemotherapy treatment has been single-agent gemcitabine, which, in a pivotal randomized trial, produced a response rate of 5%, a median survival of 5.7 months, and a clinical benefit response rate of 24% [2]. Despite numerous trials of novel agents given alone or in combination with gemcitabine, it has been quite challenging to improve upon these results [3]. A phase III trial of gemcitabine plus erlotinib demonstrated a statistically significant improvement in survival (hazard ratio 0.82) but the very modest absolute improvement in median survival (5.91 months with gemcitabine, 6.24 months with the combination), has lead some to question the clinical relevance of this observation [4]. Thus, novel agents are still clearly needed for this disease.

One of the earliest events in pancreatic carcinogenesis is mutation of the Ras oncogene, which occurs in approximately 85% of pancreatic adenocarcinomas. This, in turn, leads to constitutive activation of the downstream Raf-MAP kinase signal transduction cascade [5, 6]. This cascade may also be activated independently from Ras by extracellular signals including vascular endothelial growth factor (VEGF) [7]. In preclinical models, targeting both Raf and VEGF receptor 2 (VEGFR2) reduces growth and metastasis of pancreatic cancer cells via direct effects on tumor cells, endothelial cells and pericytes [8].

Sorafenib (Nexavar®, Bayer Pharmaceuticals) inhibits Raf serine/threonine kinase isoforms, as well as VEGFR 2 and several other receptor tyrosine kinases [9]. In preclinical models, sorafenib inhibits the growth of pancreatic cancer cell lines and xenografts [9, 10]. A phase I trial of sorafenib plus gemcitabine in advanced solid tumor patients reported by Siu and colleagues included an expanded cohort of 23 patients with pancreatic cancer. Although

there were no objective responses in this cohort, 57% percent of the pancreatic cancer patients experienced stable disease with this combination [11].

The preclinical and phase I data regarding sorafenib in pancreatic adenocarcinoma prompted us to evaluate the combination of sorafenib plus gemcitabine in a phase II trial in patients with advanced pancreatic cancer.

Patients and methods

Eligible patients had histologically or cytologically confirmed pancreatic adenocarcinoma not amenable to potentially curative surgery, measurable disease as defined by the RECIST criteria [12], ECOG performance status of 0 to 1, normal bone marrow (granulocytes $1,500/\mu\text{L}$, platelets $100,000/\mu\text{L}$), hepatic (normal total bilirubin and transaminases 2.5 times institutional upper limit of normal) and renal function (serum creatinine within normal institutional limits or creatinine clearance $60 \text{ mL/min/1.73 m}^2$). Prior radiation therapy was allowed if measurable disease was located outside of the radiation port, and more than 4 weeks had elapsed since its completion. Subjects on warfarin could participate if on a therapeutic, stable dose with an INR target 3 and no active bleeding or bleeding risk. Exclusion criteria included prior chemotherapy for pancreatic cancer, pregnancy or lactation, uncontrolled inter-current illnesses, bleeding diathesis, or immunodeficiency. All subjects provided written informed consent according to federal and institutional guidelines.

Study evaluations and treatments

Pretreatment evaluation included a medical history and physical exam, complete blood count and differential, chemistry panel, prothrombin time, pregnancy test, and a computed tomography scan of the chest and abdomen. A history and physical exam was repeated every 14 days. A complete blood count and differential and prothrombin time were repeated every 7 days, chemistry tests were repeated every 14 days. Patients received a minimum of 2 cycles unless unacceptable toxicity or rapid progression of disease occurred. Response was evaluated by CT scan according to the RECIST criteria every two cycles [12]. Confirmatory scans were to be obtained at least 4 weeks after initial documentation of an objective complete or partial response.

Drug administration

Gemcitabine, $1,000 \text{ mg/m}^2$ was given intravenously over 30 min on days 1, 8, and 15 of a 28 day cycle. Sorafenib 400 mg was administered orally two times per day on days 1 through 28 of a 28 day cycle. Subjects were instructed to swallow the tablets whole with approximately 250 mL (8 ounces) of water.

Adverse effects were graded according to National Cancer Institute Common Toxicity Criteria version 3.0. A cycle was not initiated unless the absolute granulocyte count was $1.5 \times 10^9/\text{L}$ and platelet count $100 \times 10^9/\text{L}$. Intra-cycle dose adjustments were based on counts on the day of treatment. If the granulocyte count was between 0.50 and $0.99 \times 10^9/\text{L}$, or the platelet count was between 50 to $74 \times 10^9/\text{L}$, the gemcitabine dose was reduced by 25%. Gemcitabine was held for a granulocyte count less than $0.50 \times 10^9/\text{L}$ or a platelet count $<50 \times 10^9/\text{L}$. Patients who developed neutropenic fever requiring antibiotics or bleeding

secondary to thrombocytopenia received a 25% dose reduction with the next cycle. Grade 3 non-hematologic toxicities other than nausea, vomiting, or alopecia resulted in a 25% dose reduction of gemcitabine or no treatment at the discretion of the treating physician.

The sorafenib dose was not reduced for hematologic toxicity. For grade 3 or greater non-hematologic toxicity attributable to sorafenib, the drug was held for a maximum of 21 days until recovery to grade 1 or 2, and was then reduced to 200 mg twice daily. For a recurrent grade 3 or greater toxicity, sorafenib was again held until the toxicity decreased to grade 1 or 2, and the dose was further reduced to 200 mg daily. No further dose reductions of sorafenib were permitted. If additional dose reductions were required, the patient was removed from the study.

Statistical design

The primary endpoint of this study was objective response rate (complete response + partial response) using RECIST criteria. Secondary endpoints included progression-free survival (defined as the time to disease progression or death), six-month survival and overall survival. The trial was conducted using a Simon optimal 2-stage design to test the null hypothesis that the response rate was less than or equal to 10% versus the alternative that it was at least 30% [13]. Twelve evaluable patients were to be enrolled in the first stage. If one or fewer patients had an objective response, the trial would be terminated for lack of efficacy. Otherwise, an additional 23 subjects would be accrued, and if 6 or more responses were observed among the 35 patients, the regimen would be considered worthy of further study. This design yields a 90% probability of a positive result if the true response rate is at least 30%. Progression-free and overall survival curves were constructed using the method of Kaplan and Meier [14]. Confidence intervals for the median progression-free survival and overall survival times were derived as described by Brookmeyer and Crowley [15].

Results

Patient characteristics

Seventeen patients were enrolled at 4 centers between September 2004 and December 2005. Patient characteristics are listed in Table 1. Fifty-three percent of patients were female. The median age was 62 (range 50–85). The majority of the patients (76%) had an ECOG performance status of 1. Most had metastatic disease (94%) and liver metastases (76%).

A total of 61 cycles were delivered (median 2, range 1–12). Dose reductions and delays were uncommon. Two patients required 1 dose reduction of sorafenib because of toxicity (rash and diarrhea, respectively). No permanent gemcitabine dose reductions were required.

Four patients withdrew from the study before completing 2 cycles of treatment. One patient developed a disease-related gastric outlet obstruction within 10 days of initiating therapy and was unable to continue treatment. Three patients who experienced treatment-related grade 3 toxicity within the first month withdrew from the trial and did not undergo subsequent response evaluation.

Response and survival

There were no objective responses. Three patients (18%) had stable disease as their best response, which was maintained for a median of 7.3 months (range 7.2–13.1 months). The Kaplan-Meier curve for overall survival is presented in Fig. 1. The estimated median survival was 4.0 months (95% CI, 3.4 to 5.9). The six-month survival probability was 0.23 (95% CI, 0.06 to 0.47). The median progression-free survival was 3.2 months (95% CI, 1.6 to 3.6).

Accrual to the study was terminated early due to lack of efficacy, according to the Simon 2-stage trial design.

Toxicity

All patients were evaluable for toxicity. Grade 3 and 4 toxicities are summarized in Table 2.

Hematologic toxicities were similar to those observed with single-agent gemcitabine [2]. No patient experienced neutropenic fever and few (29%) developed neutropenia. Grade 3 and 4 toxicities potentially attributable to sorafenib included thrombosis (18%), rash (12%), dehydration (12%), hand-foot syndrome (12%), hypertension (6%), and gastrointestinal bleeding (6%). Gastrointestinal perforation did not occur.

One patient who developed grade 3 hand-foot syndrome, and 2 patients who experienced grade 3 nausea, withdrew from the trial within the first month because of treatment-related toxicity.

Discussion

We evaluated the combination of gemcitabine plus the oral Raf kinase and VEGFR2 inhibitor sorafenib in patients with advanced pancreatic cancer, and observed no objective responses and a progression-free and median overall survival experience inferior to that expected with single-agent gemcitabine. We therefore conclude that this regimen is inactive in patients with advanced pancreatic cancer.

In a disease as refractory to treatment as advanced pancreatic cancer, it is, unfortunately, not particularly surprising that despite preclinical data suggesting the activity of a particular agent in this disease, and despite a phase I trial which achieved a reasonable level of stable disease, these promising findings could not be substantiated in a phase II study. Factors that may have made it more difficult for us to detect any activity of this combination include the very small sample size and the rapid disease progression exhibited by these relatively poor prognosis patients, who had predominantly metastatic disease (94%), a performance status of 1 (76%) and liver metastases (76%).

Given the poor prognosis of this patient population, it is not altogether surprising that 3 individuals were unable to tolerate the relatively modest side effects of this combination and withdrew from the trial within the first month of treatment. We also observed a relatively high incidence of grade 3 and 4 thrombosis, at 18%. Although pancreatic cancer patients are

at an increased risk of developing tumor-related hypercoagulability [16], it is likely that the combination of sorafenib plus gemcitabine increased the risk of this toxicity [17].

Our results are not substantially different from those reported by Iqbal et al [18] in 52 chemo-naïve pancreatic cancer patients who were randomized to single-agent sorafenib or sorafenib plus fixed-dose rate gemcitabine. Only 42% of patients in that study had a PS of 1, compared with 76% in our trial. There was only 1 objective response, in the combination arm. Median progression-free survival was 2.3 months for sorafenib, and 2.9 months for the combination. Median overall survival was 4.3 and 6.5 months, respectively.

Performance status is a key determinant of survival in this disease. In CALGB 80303, a phase III trial that compared gemcitabine-placebo to gemcitabine-bevacizumab, pancreatic cancer patients with a performance status of 0 survived a median of 7.9 months, compared with a median survival of only 4.8 months for patients with a PS of 1 [19]. The slightly superior outcomes observed by Iqbal et al could potentially be explained by the different percentage of patients with performance status 1 in the two studies. The relative contribution of fixed-dose rate gemcitabine to the overall survival outcome in the Iqbal trial is also uncertain. In ECOG 6201, a randomized phase III trial that compared standard 30-minute gemcitabine to fixed-dose rate gemcitabine, there was a survival difference of 1.1 months in favor of the fixed-dose rate arm, though this was not statistically significant [20].

Sorafenib inhibits the raf kinase and VEGF pathways. Although no other raf inhibitors have been evaluated in advanced pancreatic cancer, other VEGF inhibitors have already been tested. Despite promising phase II data in pancreatic cancer patients [21, 22], phase III trials of the anti-VEGF monoclonal antibody bevacizumab, and of the VEGF tyrosine kinase inhibitor axitinib have failed to demonstrate any survival benefit [19, 23, 24]. Several ongoing studies evaluate sorafenib in patients with pancreatic cancer. A double-blind placebo-controlled phase III French trial compares gemcitabine plus sorafenib to gemcitabine plus placebo. Two phase II trials explore the combination of gemcitabine, erlotinib, and sorafenib. Two other groups are evaluating the combination of gemcitabine, sorafenib, and radiotherapy in locally advanced patients. If the minimal activity we observed with this combination is confirmed in these other studies, it would be reasonable to move beyond the evaluation of VEGF inhibitors in this disease and explore other, potentially more fruitful targets.

Acknowledgments

Funding source NCI Grant N01-CM-62201

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Fig. 1.
Kaplan-Meier estimation of overall survival

Table 1

Patient characteristics

Characteristics	No. Of Patients (%)
Total	17
Age	
Median	62
Range	50–85
Sex	
Male	8 (47)
Female	9 (53)
ECOG Performance Status	
0	4 (24)
1	13 (76)
Stage	
Locally advanced	1 (6)
Metastatic	16 (94)
Sites of Disease:	
Liver	13 (76)
Lymph nodes	6 (35)
Lung	8 (47)
Peritoneum	5 (29)

Table 2

Worst toxicities per patient according to National Cancer Institute common toxicity criteria version 3.0 ($N=17$ patients)

	Grade 3 %	Grade 4 %
Hematologic		
Neutropenia	24	6
Leukopenia	18	0
Thrombocytopenia	6	0
Anemia	0	0
Neutropenic Fever	0	0
Non-hematologic		
Fatigue	18	6
Thrombosis	6	12
Anorexia	12	0
Nausea	12	0
Hand-Foot Syndrome	12	0
Rash	12	0
Diarrhea	6	0
Hypertension	6	0
Gastrointestinal bleeding	6	0
Proteinuria	0	0
Visceral perforation	0	0