Phase I trial of sunitinib and gemcitabine in patients with advanced solid tumors

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Abstract

Purpose Combining cytotoxic agents with bevacizumab has yielded significant benefits in a number of solid tumors. Combining small-molecule kinase inhibitors of VEGFR with chemotherapy has yet to demonstrate clinical benefit. The dose, schedule and agents used may be critical to the development of this combinatorial therapy.

Methods We performed a phase I trial of sunitinib and gemcitabine in patients with advanced solid tumor malignancies based on strong preclinical rationale.

Results Two different MTDs were determined. The schedule of gemcitabine 800 mg/m² on days 1, 8, 15 and sunitinib 25 mg daily was considered to be a MTD. However, omission of day 15 gemcitabine was common, and thus, a second MTD of gemcitabine of 675 mg/m² on days 1 and 8 with sunitinib 25 mg daily was determined to be the recommended phase II dose. Grade 4 neutropenia and thrombocytopenia occurred in 33 and 6 %, respectively. Grade 3/4 non-hematological toxicities were

uncommon. Four of 33 patients had a partial response. Another 11 patients had stable disease ranging from 3 to 36 months. Thus, the recommended phase II dose of this combination is gemcitabine 675 mg/m² on days 1 and 8 on an every 21-day schedule along with sunitinib 25 mg continuous daily.

Conclusions This combination is well-tolerated and has significant clinical activity.

Keywords Phase I · Sunitinib · Gemcitabine · Pancreatic cancer

Introduction

Combining cytotoxic chemotherapy with anti-angiogenic agents has yielded significant benefits in terms of improved response rates, progression-free survival and at times overall survival [1, 2]. This benefit, however, has been limited to bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF). The use of small-molecule inhibitors of VEGF, with their inherent off-target effects on other tyrosine kinases, remains problematic. For example, combining PTK787 and chemotherapy failed to improve the outcomes in advanced colon cancer [3], and the combination of sorafenib and chemotherapy yielded disappointing results in advanced non-small-cell lung cancer [4]. A potential explanation, amongst others, for this lack of improvement in benefit, may lie in issues related to scheduling, undue toxicity of the combinations or simply the disease setting in which the combination studies are conducted. Nevertheless, given the strength of the preclinical data, the rationale for combination studies remains strong in certain conditions. The combination of gemcitabine and sunitinib is a case in point. Sunitinib is an

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oral tyrosine kinase inhibitor of VEGF receptors (VEGFR-1, 2 and 3) and platelet-derived growth factor receptors (PDGFR alpha and beta). Several studies have shown the combination is superior to either agent alone in both pre-clinical in vitro and in vivo models.

The combination of gemcitabine and sunitinib has been studied both in vitro and in vivo in pancreatic adenocarcinoma xenograft models [5]. In vitro pancreatic adenocarcinoma cell lines showed significantly greater growth inhibition with the combination as compared to either agent alone. Orthotopic pancreatic cancer tumor grafts were treated with gemcitabine on a low-dose metronomic schedule (1 mg/kg daily) or a high-dose maximum-tolerated dose (150 mg/kg twice weekly) schedule with or without sunitinib. The gemcitabine metronomic schedule in combination with sunitinib significantly prolonged survival compared with either regimen alone ($P < 0.05$). Primary tumor growth was inhibited by the metronomic combination ($P = 0.03$) but not with either metronomic gemcitabine or sunitinib alone. The anti-metastatic effect of the combination of metronomic gemcitabine and sunitinib was equivalent to high-dose gemcitabine and sunitinib, suggesting that lower doses of both agents along with continuous exposure maybe equivalent to the standard maximum-tolerated dose approach of both agents. In another study, Casneuf et al. [6] treated mice bearing a pancreatic tumor xenograft with sunitinib, gemcitabine, radiotherapy, or a combination of radiation or gemcitabine with sunitinib. The authors concluded that the combination treatments, radiation and sunitinib or gemcitabine and sunitinib, resulted in a more potent anti-angiogenic and anti-tumor effect when compared to either treatment alone. In addition, there is strong rationale for continuous dosing of sunitinib. Continuous daily dosing of sunitinib, as opposed to the 4 weeks on/2 weeks off schedule used in the two indications for which sunitinib is approved, may prevent tumor re-growth during the weeks off treatment [7].

In the setting of genitourinary malignancies, this combination has also been evaluated. For example, in a bladder cancer cell line, HTB5, sunitinib was synergistic with gemcitabine by both the isobolic method and clonogenic assay [8]. A retrospective chart review was performed of 13 patients with advanced renal cell carcinoma who experienced disease progression on sunitinib and subsequently received gemcitabine 750 mg/m² i.v. on days 1 and 8 and sunitinib 37.5 mg/day on days 2–15 every 21 days [9]. Twelve of 13 patients received more than two cycles with one documented partial response and five patients with stable disease.

In this phase I trial of gemcitabine and sunitinib, we sought to determine the maximum-tolerated dose (MTD),

describe the toxicities for the combination of gemcitabine and sunitinib and recommend a phase II dose for further studies. We also sought to detect any evidence of anti-tumor activity that may lead to disease-specific evaluation in the phase II setting.

Materials and methods

Eligibility criteria

Eligibility criteria included histologically/cytologically proven solid tumor malignancy not amenable to curative therapy. Prior chemotherapy and radiotherapy were allowed with no limit on number of prior therapies. However, at least 4 weeks must have elapsed since prior anti-cancer therapies. No prior sunitinib or other anti-angiogenic therapy was allowed. Pancreatic cancer patients could be enrolled with any amount of prior therapy for unresectable or metastatic disease. Patients must have had measurable or evaluable disease by the RECIST criteria and ECOG performance status (PS) of 0–2. Cardiac criteria included a normal left ventricular ejection fraction and a QTc <500 ms. Laboratory eligibility included serum AST or ALT less than 2.5 times the laboratory upper limit of normal (ULN) or <5 times the ULN if due to underlying disease, total serum bilirubin ≤ 1.5 mg/dL, absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, hemoglobin ≥ 8.5 g/dL, calcium <12.0 mg/dL, creatinine—within normal institutional limits, or creatinine clearance >60 mL/min/1.73 m² for patients with creatinine above institutional normal. Additional eligibility criteria included the ability to swallow and retain sunitinib tablets, no known CNS metastases, no uncontrolled hypertension (>140/90), no significant cardiovascular events within 6 months and no class III or IV heart disease. The study was approved by the Case Comprehensive Cancer Center IRB, and all patients provided written informed consent.

Study design, dosage and drug administration

Sunitinib was supplied by the Division of Cancer Treatment Diagnosis and Centers, National Cancer Institute (NCI, Bethesda, MD, USA). Sunitinib was given as continuous once-daily oral dosing. Patients were required to keep a pill diary. Gemcitabine was given as 30-min intravenous infusion weekly for 3 weeks every 28 days at dose levels 1 and 2 and weekly for 2 weeks every 21 days at dose levels –1a, –1 and –2. Drug administration and dose levels are depicted in Table 1. Dose escalation followed a standard 3 + 3 design with a planned expansion of the recommended phase II dose to 10 patients.

Table 1 Dose escalation schema and enrollment

Dose level	Sunitinib dose (mg)	Gemcitabine dose (mg/m ²)	Cycles (days)	No. of patients
1	25	800 d1,8,15	28	10
2	37.5	800 d1,8,15	28	5
–1a	37.5	800 d1,8	21	3
–1	25	800 d1,8	21	5
–2	25	675 d1,8	21	10

Cohorts of 3–6 patients received therapy at each dose level based on the occurrence of dose-limiting toxicities (DLTs). DLTs (toxicities that occur within the first 28 days of treatment) were defined as any of the following that are attributable to therapy: any grade 4 toxicity (except lymphopenia or increased uric acid); any grade 3 cardiac event (except hypertension) or grade 3 venous thrombosis; hypertension unable to be controlled to <160/90 with oral medications within 4 weeks; any grade arterial thromboembolic event; any grade 3 non-cardiac toxicity that does not resolve to grade 1 within 4 weeks (except proteinuria, lymphopenia, hypophosphatemia and asymptomatic hyperamylasemia/hyperlipasemia), and proteinuria >3.5 gm/24 h. Complete blood counts were obtained weekly throughout the duration on study, and chemistry panel was obtained weekly during cycle 1 but then on day 1 of each subsequent cycle. Granulocyte colony-stimulating factors were not permitted during cycle 1. The criteria for days 8 and 15 gemcitabine treatment were as follows: if neutrophil count ≥ 1000 and platelet count $\geq 100,000$, then administer 100 % of dose; if neutrophil count 500–999 or platelet count 50,000–100,000, administer 50 % of full dose; if neutrophil count <500 or platelet count <50,000, then hold treatment altogether; if patient has any non-hematological toxicities grade 3 or 4, hold treatment; if any grade 4 toxicity has occurred during a course of therapy, next cycle's dose to be reduced to 75 % of full dose.

Patients experiencing a DLT had therapy held until toxicity resolved to grade 1 or less. Inpatient dose escalation was not permitted. The MTD level is defined as one dose level below the dose level that results in DLT in >33 % of patients. Toxicity was assessed using NCI CTCAE version 3.0, and response was evaluated using RECIST criteria version 1.0.

The primary endpoint of this trial was to determine the MTD of continuous dosing sunitinib and gemcitabine in combination in patients with solid tumors. Secondary objectives were to describe the toxicities and to observe for any anti-tumor activity.

Results

Patients

Between March 2007 and February 2010, thirty-three patients were enrolled at 5 different dose levels (Table 1). Patient characteristics are listed in Table 2. The majority of patients were female. No PS 2 patients were enrolled. Ten of the 33 patients had pancreatic adenocarcinoma of whom all but one had no prior therapy. The non-pancreatic cancer group had a median of 2 prior chemotherapy regimens. Patients received a median of 2 cycles (range 1–23) of therapy. Eleven of 33 (33 %) patients received at least 4 cycles of treatment. Nineteen of 33 (58 %) patients withdrew for disease progression while 7/33 (21 %) number withdrew for toxicity reasons. The remainder went off study for a variety of reasons including patient and physician decisions in the absence of either progression or significant toxicity.

MTD determination

The major toxicity observed was hematological in nature. At dose level 1 with gemcitabine 800 mg/m² on days 1, 8, 15 and sunitinib 25 mg daily, grade 4 neutropenia was dose limiting in 1 of the initial 3 patients. This cohort was initially expanded to a total of 6 patients with no further DLTs. Upon dose escalation to sunitinib 37.5 mg daily, we then observed 2 DLTs in 5 patients. Both DLTs were hematological in nature and consisted of a grade 4 neutropenia, and therefore dose level 1 was expanded to 10 patients with no further DLTs. Thus, the schedule of gemcitabine at a dose of 800 mg/m² on days 1, 8, 15 and sunitinib 25 mg continuous daily was considered to be the MTD. However, a significant number of patients (60 %) required omission of day 15 gemcitabine, and thus, an alternative schedule of gemcitabine on days 1 and 8 given on a 21-day schedule was explored. In this schedule along with sunitinib 37.5 mg daily, 2 of 3 patients developed dose-limiting grade 4 neutropenia. When the dose of sunitinib was reduced to 25 mg daily, again 2 of 5 patients developed grade 4 thrombocytopenia and neutropenia. One patient also developed a grade 3 decline in cardiac ejection fraction. We then decreased the dose of gemcitabine to 675 mg/m², and only 1 of 10 patients experienced a DLT, which was a grade 3 hemorrhage. Therefore, the dose of gemcitabine of 675 mg/m² on days 1 and 8 on an every 21-day schedule along with sunitinib 25 mg continuous daily without interruption was determined to be the recommended phase II dose.

Table 2 Patient characteristics

Patients	33
Median no. of courses	2 (range 1–23)
Median age	57 (range 39–75)
Gender M/F	11/22
ECOG PS 0/1	8/25
Histologies	
Pancreatic adenocarcinoma	10
Non-small-cell lung cancer	2
Ovarian	2
Cholangiocarcinoma	2
Uterine	2
Mesothelioma, adrenocortical carcinoma, germ cell tumor, adenoid cystic carcinoma, head and neck squamous cell, thymoma, thymic carcinoma, osteogenic sarcoma, soft tissue sarcoma, breast, pancreatic neuroendocrine, medullary thyroid, carcinoma of unknown primary, neuroendocrine carcinoma of unknown primary, papillary thyroid	15 (1 of each)
Median no. of prior therapies	
Pancreatic patients	0 (range 0–1)
Non-pancreatic patients	2 (range 0–6)

Overall safety

The overall toxicity of the regimen is depicted in Table 3. Thirty-three percent of patients developed grade 4 neutropenia. However, this neutropenia was generally short-lived, and only 2 episodes of febrile neutropenia were observed in the 145 total cycles administered on this trial. Grade 4 thrombocytopenia occurred in 6 % of patients. Grades 3 and 4 non-hematological toxicities were generally uncommon. Only 9 % of patients developed grade 3 hypertension. Grades 1 and 2 non-hematological toxicities were common including electrolyte abnormalities and fatigue.

Efficacy

Clinical efficacy is depicted in Table 4. Four of 33 patients experienced a confirmed partial response. Two of these patients had pancreatic cancer (two of ten) and both were chemotherapy-naïve patients. Another patient with thymic carcinoma had previously received carboplatin and paclitaxel as first-line therapy and another phase I trial with methoxyamine and temozolomide prior to enrolling on this trial. She went on to receive 17 cycles of therapy and was eventually taken off due to persistent diarrhea. A fourth patient with pancreatic neuroendocrine carcinoma had a response. The time to progression for these 4 partial responders ranged from 9 to 23 months. Of interest is that

the responses were not dose related with 2 responses seen at dose level 1 and two of them at dose level –2. Another 11 patients had stable disease ranging from 3 to 36 months. The patient with disease stabilization for 36 months had a malignant thymoma that previously failed to respond to cisplatin and etoposide.

Discussion

In this phase I study, we determined the MTD of gemcitabine and sunitinib. Two different MTD levels were determined based on scheduling of the agents. In the first with gemcitabine 800 mg/m² on days 1, 8, and 15 on an every 28-day cycle, sunitinib 25 mg daily could be administered. This schedule, however, was associated with a significant number of patients omitting day 15 of gemcitabine and therefore is not our recommended phase II dose. The second MTD level was gemcitabine at 675 mg/m² on days 1 and 8 along with sunitinib 25 mg daily in a 21-day cycle. We recommend this dose for future phase II trials as day 8 gemcitabine was rarely omitted. Our regimen was frequently associated with grades 3 and 4 hematological toxicities; however, only 2 instances of febrile neutropenia and 1 instance of bleeding were observed. A pharmacological interaction between the two agents is unlikely given the different routes of metabolism for sunitinib and gemcitabine. It is clear that the combination is clearly more myelosuppressive than gemcitabine alone. However, the hematological changes had little clinical consequence. In comparison, a phase I trial of cisplatin/gemcitabine and sunitinib in advanced NSCLC has also been conducted [10]. In this study, sunitinib 37.5 or 50 mg/day was given intermittently for 2 weeks with 1 week off or 25 mg continuous daily dosing. Gemcitabine (1000 or 1250 mg/m² days 1, 8) and cisplatin (80 mg/m² day 1) were given at standard doses. In this study as well, myelosuppression was dose limiting with the need for frequent dose delays. This finding of a VEGF inhibitor adding to the myelosuppression of chemotherapy is well described [2, 4]. It is thus likely that the additive myelosuppressive effect of sunitinib is due to on-target effects on VEGF signaling. The observed hypertension and hand/foot syndrome rates were no different than what would be expected with sunitinib alone. Other non-hematological toxicities were grades 1 and 2 and generally reversible.

The anti-tumor activity observed was encouraging and occurred mainly in diseases for which gemcitabine or sunitinib may have activity, namely pancreatic adenocarcinoma and pancreatic neuroendocrine carcinoma, respectively. Single-agent sunitinib has minimal activity in pancreatic adenocarcinoma, but synergy may exist between gemcitabine and sunitinib, as suggested by preclinical

Table 3 Summary of drug related adverse events and laboratory abnormalities per NCI version 3.0 in all cycles (patients = 33; cycles = 145)

Adverse event	Toxicity grade			
	1	2	3	4
Hematological				
Neutropenia	1 (3 %)	3 (9 %)	7 (21 %)	11 (33 %)
Febrile neutropenia	0	0	2 (6 %)	0
Thrombocytopenia	11 (33 %)	8 (24 %)	4 (12 %)	2 (6 %)
Anemia	9 (27 %)	9 (27 %)	4 (12 %)	0
Non-hematological				
AST/ALT	10 (30 %)	4 (12 %)	0	0
Bilirubin	1 (3 %)	0	0	0
Alkaline phosphatase	4 (12 %)	2 (6 %)	1 (3 %)	0
Nausea	8 (24 %)	5 (15 %)	1 (3 %)	0
Vomiting	7 (21 %)	4 (12 %)	1 (3 %)	0
Diarrhea	7 (21 %)	4 (12 %)	1 (3 %)	0
Constipation	0	2 (6 %)	0	0
Anorexia	8 (24 %)	2 (6 %)	0	0
Hemorrhage	0	0	1 (3 %)	0
Thromboembolic	0	0	2 (6 %)	0
Hypertension	0	1 (3 %)	3 (9 %)	0
Decreased cardiac EF	0	0	1 (3 %)	0
Fever	4 (12 %)	0	0	0
Creatinine	4 (12 %)	0	0	0
Albumin	4 (12 %)	6 (18 %)	0	0
Hyponatremia	2 (6 %)	0	1 (3 %)	0
Hypokalemia	6 (18 %)	0	2 (6 %)	0
Hypomagnesemia	11 (33 %)	0	0	0
Hypophosphatemia	1 (3 %)	2 (6 %)	1 (3 %)	0
Hypocalcemia	5 (15 %)	2 (6 %)	0	0
Headache	2 (6 %)	0	0	0
Neuropathy	2 (6 %)	1 (3 %)	0	0
Skin rash	3 (9 %)	1 (3 %)	1 (3 %)	1 (3 %)
Hand and foot syndrome	0	1 (3 %)	0	0
Allergic reaction	0	1 (3 %)	0	0

Data presented as highest grade in each patient irrespective of dose level

studies. A reasonable drug development strategy would be to consider a randomized phase II trial of gemcitabine with or without sunitinib in advanced pancreatic adenocarcinoma. This approach utilizing gemcitabine with or without another agent has been questioned in the pancreatic cancer research community, in part due to three negative, large, randomized trials of gemcitabine single agent compared to gemcitabine plus erlotinib [11], gemcitabine plus cetuximab [12] and gemcitabine plus bevacizumab [13]. Of interest is the lack of benefit seen with the anti-angiogenic agent bevacizumab, and the signal of possible activity reported here with sunitinib, a more promiscuous angiogenesis inhibitor. Our recommended phase 2 dose includes relatively low doses of gemcitabine and sunitinib. Given

the responses seen at the lower doses of gemcitabine, the contribution of continuous sunitinib dosing needs to be ascertained. In an orthotopic pancreas cancer model, mice administered metronomic gemcitabine with daily sunitinib displayed superior tumor control and survival compared to metronomic gemcitabine alone ($P = 0.04$) or sunitinib alone ($P = 0.002$), with a suggestion of synergy at the lower doses of the combination [14]. A single case report of a 43-year-old white man diagnosed simultaneously with metastatic pancreatic adenocarcinoma and localized renal cell carcinoma describes treatment with a combination of gemcitabine and sunitinib [15]. This patient had a radiographic response in both malignancies and had prolonged progression-free survival of 26 weeks; side effects were

Table 4 Clinical efficacy

Response	Tumor type	Dose level	No. cycles received	Time to progression (months)	# Prior regimens
Partial response	Pancreatic adenocarcinoma	1	23	23	0
	Pancreatic adenocarcinoma	1	8	9	0
	Pancreatic neuroendocrine	−2	11	9	0
	Thymic Carcinoma	−2	17	13	3
Stable disease	Pancreas	2	4	5	0
	Thymoma	2	5	36	1
	Pancreatic adenocarcinoma	1	3	3	1
	Cholangiocarcinoma	1	11	12	0
	Osteogenic sarcoma	1	6	6	2
	Pancreatic neuroendocrine	−1	4	4	2
	Uterine	−1	6	5	2
	Papillary thyroid	−1	8	7	2
	Breast	−1a	6	5	5
	Pancreatic adenocarcinoma	−2	4	9	0
	Ovary	−2	4	4	0

manageable and included grade 3 neutropenia and grade 2 hypertension. In our study, a patient with pancreatic neuroendocrine carcinoma had a prolonged partial response. In this setting, sunitinib has known activity, and therefore, the contribution of the combination therapy to the response seen is unknown. Thus, a randomized phase II trial of sunitinib with or without gemcitabine in pancreatic neuroendocrine carcinoma should also be considered. In our study, a patient with heavily pretreated thymic carcinoma had a prolonged response to this regimen. Based on the observed activity, phase II trials of this regimen in thymic carcinoma may also be indicated.

Conflict of interest None.

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