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ORIGINAL ARTICLE

A phase II study of bevacizumab plus erlotinib for gemcitabine-refractory metastatic pancreatic cancer

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Abstract
Purpose No standard of care exists for patients with metastatic pancreatic cancer following progression on first-line chemotherapy. Based on potential for additive or synergistic activity by concurrent inhibition of VEGF and EGFR, we conducted a phase II study evaluating the combination of bevacizumab plus erlotinib in this patient population.
Methods Patients with metastatic pancreatic adenocarcinoma, ECOG performance status 0–1, and previous exposure to 1–3 systemic therapies (at least one gemcitabine-based) were eligible. Treatment consisted of bevacizumab 15 mg/kg every 21 days plus erlotinib 150 mg daily.
Results Thirty-six patients were enrolled, including eight who had previously received VEGF-targeted therapy and nine prior erlotinib. Median number of treatment cycles was 2 (range, 1–7). Common toxicities included rash (72%), diarrhea (25%), venous thromboembolic events (15%), and hypertension (11%). One patient demonstrated partial response and seven others stable disease for >2 cycles. CA19-9 decline ≥25% was observed in 4/26 patients with baseline levels >2*x* ULN. Estimated median time to progression was 40 days (95% CI, 35–41 days) and median survival 102 days (95% CI, 74–117 days), with a 6-month survival rate of 22%. Baseline concentration of circulating endothelial cells ($CD45^-/CD34^+/CD31^+$) was inversely associated with overall survival.
Conclusions The combination of bevacizumab and erlotinib is safe but relatively ineffective in patients with gemcitabine-refractory metastatic pancreatic cancer. Future studies should focus on refining subsets of patients in this challenging population likely to benefit from treatment beyond first-line.

Keywords Bevacizumab · Circulating endothelial cells · Erlotinib · Pancreatic cancer · Phase II · Refractory

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Introduction

Pancreatic cancer was responsible for an estimated 35,240 deaths in the United States in 2009 and, stage for stage, is associated with the lowest survival rate of any cancer site [1]. Over the past decade, gemcitabine-based regimens have been the mainstay of treatment for patients diagnosed with advanced stages of disease. A few gemcitabine-containing combinations have demonstrated modest improvements compared to gemcitabine alone, particularly in patients with good performance status [2]; nevertheless, median survival rates even with these regimens remain in the range of only 6–9 months [3–6]. At the time of disease progression on front-line therapy, only approximately half of patients are suitable for further treatment [7], reflecting the inanition and rapid clinical deterioration that so often characterizes these individuals. There are few effective alternative therapeutic options in this salvage setting, with no established standard of care.

Bevacizumab and erlotinib, both independently and concurrently, have been added to gemcitabine in clinical trials for patients with previously untreated advanced pancreatic cancer [8, 9]. Erlotinib, an orally bioavailable small molecule inhibitor targeting the epidermal growth factor receptor

(EGFR), gained FDA approval for this indication based on a statistically significant but modest improvement in survival when added to gemcitabine [5]. Dual inhibition of the EGFR and vascular endothelial growth factor (VEGF) pathways may confer additive or even synergistic benefit [10, 11], and the combination of bevacizumab and erlotinib has shown evidence of clinical activity in a variety of other solid tumors [12–15]. On these bases, we conducted a non-randomized, single-arm phase II study evaluating the combination of these two agents for patients with gemcitabine-refractory, metastatic pancreatic cancer.

Methods

Patient eligibility

Patients were eligible for this study if they were 18 years of age or older, had an ECOG performance status of 0 or 1, and had a confirmed diagnosis of pancreatic adenocarcinoma with radiographic or biopsy-proven evidence of extrapancreatic metastases (stage IVb). Those with locally advanced unresectable disease only were not eligible. Extrapancreatic metastases did not have to be measurable by formal RECIST criteria. Patients must have received at least one, but no more than three, prior systemic therapies for advanced disease (locally advanced or metastatic), at least one of which was gemcitabine-based. Chemotherapy given in the adjuvant setting either alone or concurrently with radiation did not count as prior therapy as long as progressive disease occurred >6 months following completion of treatment. Patients were allowed to have received either an anti-VEGF or an anti-EGFR agent as part of their prior therapy, but not both.

Adequate hematologic, renal, and hepatic function was required as defined by the following: absolute neutrophil count $\geq$ 1,500/μl, platelet count $\geq$ 100,000/μl, hemoglobin $\geq$ 9 g/dl, an international normalized ratio $\leq$ 1.5 (except for participants receiving full-dose warfarin at the time of study entry), creatinine level $\leq$ 2.0 mg/dl, bilirubin level $\leq$ 2.0 mg/dl, and transaminases $\leq$ 2.5x ULN ($\leq$5x ULN in patients with liver metastases). Any major surgical procedure had to be completed more than 28 days from the time of study entry. Female patients of childbearing potential must have had a negative urine pregnancy test before study entry.

Patients were excluded if they had central nervous system metastases, another active malignancy, or any history of other malignancy within the past 5 years except for non-melanoma skin cancer and carcinoma in situ of the cervix. A history of myocardial infarction or stroke within the last 6 months, uncontrolled hypertension (blood pressure of >150/100 mmHg on medication), unstable angina, New York Heart Association Grade II or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication, grade II or greater peripheral vascular disease, non-healing wounds, ulcers, or bone fractures, or evidence of bleeding diathesis or coagulopathy, all represented additional exclusion criteria. Moreover, patients with any concurrent medical condition that, in the opinion of the treating physician, would constitute a hazard for participation in this study, were also excluded. Patients on therapeutic doses of warfarin or low-molecular weight heparin were eligible as long as they had been on a stable dose for at least 28 days with no further clotting or bleeding complications.

Study design and treatment

This was a phase II, single center, open-label, single-arm study. The trial was approved by, and conducted in accordance with the ethical standards of, the University of California San Francisco Committee on Human Research. All patients signed informed consent prior to study participation. Patients received bevacizumab 15 mg/kg as a 60–90 min infusion every 21 days (representing one treatment cycle) and erlotinib 150 mg by mouth daily, noting that this erlotinib dose is higher than that approved by the FDA for pancreatic cancer when administered concurrently with gemcitabine.

Dose adjustments in erlotinib were made depending on the toxicity observed with each treatment cycle. The erlotinib dose was reduced to 100 mg daily and then 50 mg daily based on the development grade 3 diarrhea, intolerable rash, or other grade 3/4 adverse events. No dose re-escalation was permissible. Erlotinib was discontinued for grade 4 diarrhea or evidence of interstitial lung disease. There was no reduction in the bevacizumab dose allowed. Bevacizumab was discontinued for grade 4 hypertension, uncontrolled grade 3 hypertension despite maximal medical therapy, grade 4 or repeated grade 3 bleeding episodes, symptomatic grade 4 pulmonary embolism, any arterial thromboembolic event, grade 4 proteinuria, gastrointestinal perforation, or wound dehiscence requiring surgical or medical intervention. Bevacizumab was held in patients who developed a grade 3 or asymptomatic grade 4 deep venous thrombosis, but could be resumed once patients were on a stable dose of anticoagulant without any evidence of bleeding for >1 week.

Patients who could not resume study treatment for 3 weeks from the time of last treatment because of unresolved toxicities were removed from the study. Additionally, patients were removed from study if any of the following occurred: progressive disease based upon radiographic and/or clinical criteria, patient withdrawal of consent, or non-compliance.

Evaluation

The primary efficacy measure was overall survival rate at 6 months, measured from the first date of study treatment to the date of death. In the absence of confirmation of death, survival was censored at the last date of follow-up. Secondary efficacy measures included time to tumor progression (TTP), objective response rate by RECIST criteria in patients with measurable disease at baseline, and CA19-9 biomarker response. TTP was defined as the time from initial therapy to the first objective documentation of tumor progression (for patients with measurable disease) or to the date of death, if death was ascribed to progression of disease. Patients initially without measurable disease were included in the TTP analysis based either on the appearance of new measurable lesions or on strongly suggestive radiographic evidence of progression of non-measurable disease (e.g. peritoneal carcinomatosis). TTP was censored for patients who did not have objective evidence of tumor progression at the time of study discontinuation or who died of causes unrelated to pancreatic cancer. CA19-9 biomarker response was defined as a reduction in CA 19-9 values by $\geq$50% from baseline in those patients with a twofold or greater elevation at baseline. Changes in CA 19-9 alone were not the sole basis for making decisions regarding whether to continue or stop treatment.

Safety was evaluated in terms of adverse events and clinical laboratory abnormalities, graded according to the National Cancer Institute common toxicity criteria (version 2.0). Adverse event assessments were performed on day 1 of each treatment cycle and at the end of treatment. Hematologic, renal, and hepatic function tests were performed at baseline, on day 1 of each treatment cycle and at the end of treatment.

Statistical methods

The primary endpoint in this study was 6-month survival rate. The sample size was based on the presumption that a survival rate of 30% at 6 months would be indicative of significant biological activity of this regimen and warrant further investigation. With 40 patients, if a 6-month survival of 30% (12/40) was observed, the 95% confidence interval for that proportion would be 17–47%, and for any value the CI would be no wider than the observed $\pm$16% points. Early stopping rules were in place for both safety (i.e., if >3 of the first 10, or 6 of the first 20, patients experienced serious adverse events leading to removal from study) and efficacy (if fewer than 4 of the first 18 patients were alive at 6 months).

Time to event endpoints was derived by Kaplan–Meier methods. Radiographic response, treatment administration, adverse events, and laboratory abnormalities were summarized descriptively.

Correlative studies

Isolation and enumeration of circulating endothelial cells (CECs) were performed by flow cytometric analysis both at baseline and, when feasible, following two treatment cycles. Fluorescence-activated cell sorting was performed using a FACS Calibur (Becton–Dickinson) with four-color option to identify tumor cells based on surface marker phenotype. CECs were classified based on two separate phenotypes: $CD45^-/CD34^+/CD31^+/thioflavin^+$ and $CD45^-/CD34^+/CD146^+/thioflavin^+$.

In a subset of patients, CECs were also measured using the CellSearch System (Veridex, LLC, Warren, NJ, USA). This involved an initial immunomagnetic enrichment step in which cells were captured using ferrofluids coated with CD146 antibodies. The CD146-enriched, fluorescently labeled cells were identified as CECs using the CellSpotter Analyzer, a semiautomated fluorescence-based microscopy system, when the cells exhibited the $DAPI^+/CD105^+/CD45^-$ phenotype.

Results

Patient characteristics

Thirty-six patients were enrolled on study between March 2006 and December 2008. Accrual slowed dramatically after June 2008, following results from two large randomized trials (CALGB 80303 and AVITA) that demonstrated no significant survival benefit of bevacizumab when added to gemcitabine-based regimens in advanced pancreatic cancer. The decision was made to stop study enrollment in December 2008, with 36 of the planned 40 patients accrued.

Baseline characteristics are listed in Table 1. There was an approximately even distribution of patients with ECOG performance status zero versus one. Most patients had received exactly one prior line of systemic therapy, including nine and eight patients who had received either erlotinib or anti-VEGF therapy, respectively. The majority of patients had an elevated serum CA19-9 level greater than twofold the upper limits of normal. One patient remains alive at the time of the writing of this manuscript.

Treatment administration and safety

Table 2 provides a summary of study treatment. The maximum number of treatment cycles delivered on this trial was 7, with the majority of patients receiving two cycles (at which time point the first formal response evaluation was undertaken) or fewer. Greater than 80% of patients were discontinued from study treatment because of progressive disease.

Table 1 Patient baseline characteristics

Characteristic	Patients, no., % ($N = 36$)
Median age, years (range)	60 (36–82)
Sex	
Male	20 (56)
Female	16 (44)
Ethnicity	
Caucasian (non-Hispanic)	28 (78)
Hispanic	3 (8)
African-American	3 (8)
Asian-American/Pacific Islander	3 (8)
ECOG performance status	
0	16 (44)
1	20 (56)
Number of prior lines of systemic therapy	
1	24 (67)
2	9 (25)
3	3 (8)
Prior VEGF/VEGFR therapy	8 (22)
Prior EGFR therapy	9 (25)
Prior Whipple resection	8 (22)
Prior radiation	10 (28)
Elevated baseline CA19-9 (>2*x* ULN)	26 (72)

Table 2 Summary of study treatment

Median no. of treatment cycles (range)	2 (1–7)
Patients receiving two or fewer cycles	28/36 (78%)
Patients requiring dose reduction in erlotinib	5 (14%)
Reasons for study discontinuation, no. (%)	
Progressive disease	29 (81%)
Self-withdrawal due to poor tolerance	2 (6%)[a]
Adverse event	4 (10%)[b]
Prolonged treatment interruption for palliative XRT	1 (3%)

[a] One patient secondary to asthenia and grade 3 rash; one patient secondary to asthenia

[b] One patient with grade 3 upper GI bleed; one patient with unexplained severe abdominal pain not related to disease progression; one patient with pulmonary embolism and increasingly symptomatic pleural effusion; one patient with bilateral DVTs (accompanied by asthenia)

Cutaneous toxicity and diarrhea were the most common adverse events observed, although in only one patient each were these classified as grade 3. Erlotinib dose was reduced in five patients, primarily secondary to cutaneous toxicity; prophylactic use of topical emollients, steroids, and antibiotics was not mandated by study protocol. Other bevacizumab-associated adverse events observed on the study included hypertension, venous thromboembolic events, and gastrointestinal bleeding. There were no bowel perforations, arterial thromboembolic events, or cases of interstitial pneumonitis. No patient deaths were ascribed to be a direct result of study treatment. Table 3 provides a summary of major toxicities.

Table 3 Treatment-associated toxicity

Toxicity	No. (%)
Rash	26 (72)
Grade 1	6 (17)
Grade 2	19 (53)
Grade 3	1 (3)
Diarrhea	9 (25)
Grades 1–2	8 (22)
Grade 3	1 (3)
Hypertension (grade 3)	4 (11)
Gastrointestinal bleeding	2 (6)
Grade 1	1 (3)[a]
Grade 2	0
Grade 3	1 (3)[b]
Venous thromboembolic events	5 (14)
Grade 2	2 (6)[c]
Grade 3	1 (3)
Grade 4 (pulmonary embolism)	2 (6)
Dyspnea	2 (6)[d]
Pancreatogastric fistula	1 (3)
Suspected hemorrhage into intrapulmonic metastases	1 (3)

[a] Rectal bleeding likely 2o to hemorrhoids

[b] Upper GI bleed 2o to duodenal ulcers. Patient had been on low-molecular weight heparin at the time

[c] One had a Mediport-associated deep vein thrombosis, and one had an asymptomatic SMV thrombosis

[d] Etiology was uncertain in these two cases. There was no evidence of interstitial pneumonitis

Efficacy

Eight of 36 patients (22.2%) demonstrated disease control for >2 cycles on study treatment, including a single patient showing a partial response in measurable hepatic metastases and two others with a reduction in non-measurable disease sites (Table 4). Kaplan–Meier curves for time to progression and overall survival are shown in Fig. 1a and b, respectively. In terms of the primary efficacy measure (overall survival rate at 6 months), 8 of 36 patients (22.2%) achieved this threshold.

Correlative studies

Peripheral blood samples were collected from 31 patients at baseline for CEC measurements by flow cytometry. In general,

Table 4 Efficacy results

Efficacy measure	Number
Objective response by RECIST	1 PR
Stable disease >2 cycles	7 (19%)[a]
CA19-9 biomarker decline of ≥25% (patients with >2*x* ULN as baseline, *N* = 26)	4 (15%)
Estimated median TTP, days (95% CI)	40 (35–41)
Estimated median overall survival, days (95% CI)	102 (74–117)
6-Month survival rate, %	8/36 (22%)

[a] Includes one patient with a decrease in size of peritoneal metastases, and one with decreased ascites

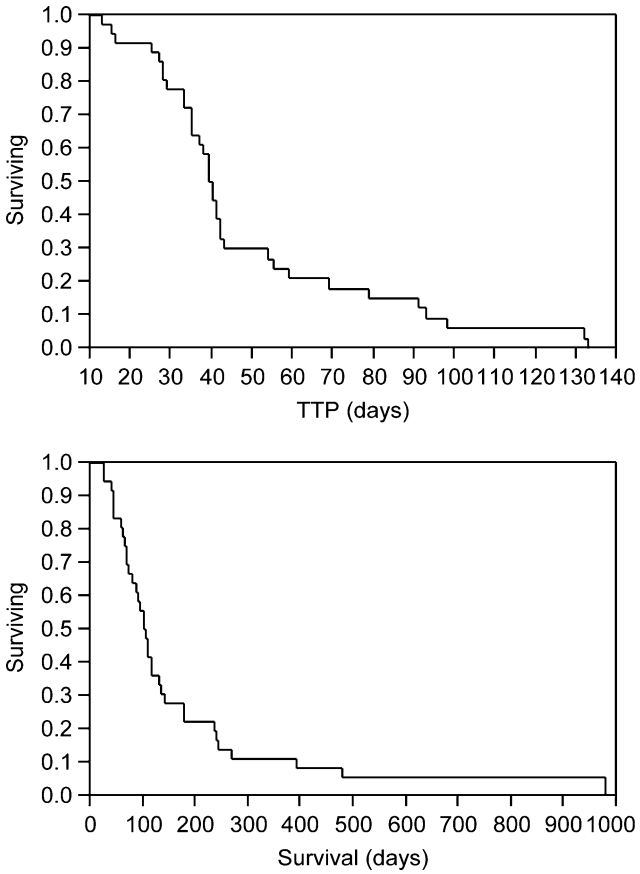

Fig. 1 Kaplan–Meier curves demonstrating time to tumor progression (**a**) and overall survival (**b**)

a higher CEC concentration was found by $CD34^+/CD31^+$ immunophenotyping than by $CD34^+/CD146^+$ immunophenotyping (median concentration, 11.9 $CD34^+/CD31^+$ cells/μl (range, 0.5–54.2) vs. 2.0 $CD34^+/CD146^+$ cells/μl (range, 0.2–14.9)). In 27 patients, the CellSearch automated system was also used, with a median of 10.0 CECs/μl detected (range, 3.0–66.3). There was no correlation observed between these methods. Using Cox proportional hazard regression, only baseline concentration of $CD34^+/CD31^+$ cells was inversely associated with overall survival ($P = 0.0217$). Because the majority of patients showed disease progression within the first two treatment cycles, we were able to perform protocol-specified follow-up CEC collection on only 11 patients, a sample size too small to correlate with any clinical outcome measures.

Discussion

There is a relative paucity of published studies evaluating the safety and effectiveness of chemotherapy regimens in patients with advanced pancreatic cancer who have progressed following first-line therapy. Several selected studies are shown in Table 5, which highlights the low response rates and exceedingly poor survival that is characteristic for these patients. Recently, results from one of the largest studies conducted to date for the second-line treatment of advanced pancreatic cancer (CONKO-003) suggested that a weekly regimen called OFF (oxaliplatin, 5-FU given as a 24 h infusion, and folinic acid) may improve patient outcomes [16]. In this randomized study of 165 patients, OFF demonstrated superiority to 5-FU/folinic acid alone in terms of both progression-free survival (13 vs. 9 weeks, $P = 0.012$) and overall survival (26 vs. 13 weeks, $P = 0.014$).

However, given the marginal performance status and inanition so often manifest in these patients, a therapeutic strategy using exclusively non-cytotoxic targeted agents represents an attractive alternative. Our selection of erlotinib and bevacizumab for this study was based upon preclinical and clinical evidence that these two agents, both separately and in combination, could be well-tolerated and potentially effective in this disease context. EGFR and VEGF share common downstream signaling pathways. VEGF is down-regulated by EGFR inhibition, and blockade of VEGF may also inhibit EGFR autocrine signaling [17–19]. Several preclinical studies have reported at least additive, if not synergistic, effects of anti-EGFR and anti-VEGF agents when used in combination [10, 11]. In the clinical arena, phase II trials of bevacizumab/erlotinib have been conducted in breast [14], renal cell [12], head and neck [13], and non-small cell lung cancers [15]. In NSCLC, the regimen appears to be at least as effective as chemotherapy plus bevacizumab and superior to chemotherapy alone [15].

Specific to pancreatic cancer, erlotinib has demonstrated a significant survival benefit when added to gemcitabine in a placebo-controlled phase III trial in patients with advanced, untreated disease, although the absolute magnitude of benefit was quite modest (an improvement in median survival of 0.4 months) [5]. Moreover, at the time of conception of our study, bevacizumab was garnering a

Table 5 Previous studies in gemcitabine-refractory advanced pancreatic cancer

Regimen	# pts	RR (%)	Median survival (mos)	References
Paclitaxel	18	5.6	4.0	[24]
Raltitrexed	19	0	4.3	[25]
Raltitrexed/irinotecan	19	16	6.5	[25]
5FU/LV/oxaliplatin	30	23.3	5.8	[26]
	76	N/A	5.9	[16]
5-FU/LV	84	N/A	3.0	[16]
9-Nitrocamptothecin	58	7	3.0	[27]
Pemetrexed	52	3.8	4.6	[28]
Capecitabine/erlotinib	30	11	6.7	[29]
Docetaxel/irinotecan	14	0	4.4	[30]

great deal of interest in pancreatic cancer based upon the putative role of VEGF signaling in this disease and promising results from a phase II trial. In that study, bevacizumab was evaluated in the front-line setting in combination with gemcitabine, with a progression-free survival of 5.4 months and median survival of 8.8 months [20]. This led to two separate phase III trials, one conducted in the United States (CALGB 80303) and the other in Europe (AVITA), in which bevacizumab was added to gemcitabine and gemcitabine/erlotinib, respectively. Disappointingly, neither of these trials showed a significant survival benefit for the bevacizumab-containing arms, although the AVITA trial did demonstrate an improvement in PFS with the addition of bevacizumab (4.6 vs. 3.6 months; $P = 0.0002$) [8, 9]. Once those results became publicly available, enrollment to our study declined, ultimately leading to its closure slightly before reaching its intended accrual goal.

While the combination of bevacizumab and erlotinib did benefit a small number of patients in our trial, the primary endpoint was not met, with only 22% of patients remaining alive 6 months from the time of study entry. Moreover, the vast majority of patients discontinued therapy within 6 weeks due to disease progression, typically accompanied by a rapid clinical decline. Our results parallel those recently reported in a CALGB trial (80603), which also evaluated a non-cytotoxic regimen in gemcitabine-refractory pancreatic cancer [21]. In that trial, which investigated the oral VEGFR inhibitor sunitinib ($N = 77$), median PFS was 1.4 months, and OS was 3.2 months, outcomes strikingly similar to ours.

We did also evaluate the prognostic value of circulating endothelial cells (CECs) in our study population using several different methods. CECs have been shown to correlate significantly with patient outcomes in other solid malignancies in which bevacizumab has been evaluated, including rectal and breast cancer [22, 23]. While we did detect a statistically significant inverse association between baseline CEC concentration (as defined by cells with a $CD45^-/CD34^+/CD31^+$ immunophenotype) and overall survival, the utility of this test both as a prognostic marker and as a tool to assess the effectiveness of ongoing anti-angiogenic treatment in pancreatic cancer requires further validation.

In summary, these data demonstrate that a "targeted-only" approach to pancreatic cancer, while conceptually appealing, should be considered a work in progress and cannot yet be recommended, with results that are currently inferior to those reported with cytotoxic regimens. Particularly in the second-line setting and beyond, the challenge remains to find safe and effective therapies for this fragile patient population in whom judicious selection of therapeutic agents is especially critical.

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