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ORIGINAL ARTICLE

Bevacizumab plus gemcitabine and oxaliplatin as first-line therapy for metastatic or locally advanced pancreatic cancer: a phase II trial

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Abstract
Purpose The gemcitabine and oxaliplatin (GEMOX) has yielded among the longest progression-free survival durations in patients with advanced pancreatic cancer (APC). We postulated that adding bevacizumab would increase the effectiveness of GEMOX.
Methods Eligible patients had stage III or IV pancreatic cancer, ECOG PS 0-2, and no prior gemcitabine. Treatment included 1,000 mg/m^2 intravenous gemcitabine over 100 min on day 1, 10 mg/kg intravenous bevacizumab on day 1, and 100 mg/m^2 oxaliplatin given on day 2. Cycles were repeated every 2 weeks. CT imaging was performed every 6 weeks.
Results Fifty patients were enrolled: 14 had stage III disease, the remainder stage IV. Median age was 59 years. Fourty-five patients were ECOG 0-1. The grade 3–4 toxicity rate was 94%; fatigue (47%) and nausea (40%) were frequent. One patient died after a bowel perforation; a second died of a CVA. The median PFS was 4.9 months; median survival was 11.9 months; 1 year survival was 42%. Locally advanced patients lived 12.8 months; metastatic patients lived 10.2 months. Patients developing grade 3 hypertension were more likely to have a radiologic response ($P = .012$); survival among the top and bottom quintiles of hypertension was 14.7 and 6.2 months, respectively. Survival correlated with baseline CA 19–9 ($P = .004$) and radiologic response. The overall response rate was 36%; 34% demonstrated stable disease.
Conclusions The GEMOX/bevacizumab regimen demonstrated an excellent median overall survival but did not meet our objective of a 14 month median survival. Toxicity was significant. We do not recommend further evaluation of this regimen.

Keywords Pancreatic cancer · Adenocarcinoma · Pharmacotherapy · Antibodies · Monoclonal · Clinical trial · Chemotherapy

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Introduction

Pancreatic adenocarcinoma is now the fourth-leading cause of cancer-related deaths in the United States, where more than 30,000 people are diagnosed with it annually, almost all of whom die of this disease [1]. Roughly, 85% of patients present with unresectable or metastatic disease. Median survival duration ranges from 8 to 12 months and 6 to 9 months in each of these groups, respectively [2].

Chemotherapy is the mainstay of treatment for advanced pancreatic cancer. Since 1997, gemcitabine has emerged as the standard systemic drug delivered to patients with advanced pancreatic cancer as a result of a phase III comparison with 5-fluorouracil (FU) [3]. Efforts to improve gemcitabine's efficacy have focused on the

addition of other cytotoxic agents (e.g., oxaliplatin [2], cisplatin [4], irinotecan [5], pemetrexed [6], fluorouracil [7], capecitabine [8]) or of molecular agents (e.g., erlotinib [9]) to gemcitabine. At the time this study was designed, the most promising combination appeared to be with oxaliplatin. Preclinical data suggested that oxaliplatin was superior to cisplatin in achieving cell-growth inhibition and apoptosis [10]. Louvet and colleagues [2] found that this regimen (GEMOX) resulted in a response rate of 30%, prompting a larger, randomized phase III trial. This trial [11] compared GEMOX with gemcitabine alone in patients with advanced pancreatic cancer. GEMOX was superior to gemcitabine alone in terms of response rate (26.8% vs. 17%), clinical benefit response (38% vs. 26%), and median progression-free survival duration (5.8 vs. 3.7 months). The median survival duration was also better with this combination (9 months vs. 7 months), but this finding did not reach statistical significance ($P = .13$).

Researchers postulated that bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, would enhance gemcitabine's efficacy in patients with pancreatic cancer. At the time this study was designed, preliminary results of a phase II trial of gemcitabine and bevacizumab in APC suggested improved median overall survival duration over gemcitabine monotherapy [12]. We therefore hypothesized that the addition of both a cytotoxic agent (oxaliplatin) and a promising molecular agent (bevacizumab) to gemcitabine would lead to a higher objective response rate and longer survival than either doublet. If so, this would represent a step forward in pancreatic cancer treatment.

Patients and methods

Patient eligibility and study design

This was an open-label phase II study of patients with locally advanced or metastatic pancreatic cancer not previously treated with gemcitabine, oxaliplatin, or bevacizumab. The protocol was approved by the respective IRBs of the two participating institutions—the U.T. M. D. Anderson Cancer Center, and the University of Oklahoma Health Sciences Center. Inclusion criteria were age of at least 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and measurable metastatic or locally advanced disease. Patients with relapsed pancreatic cancer were eligible if prior treatment (surgery with or without 5-FU–based adjuvant therapy, including radiation) was completed more than 6 months prior to enrollment. However, prior therapy for locally advanced or metastatic disease was not allowed. Other inclusion criteria included relief of obstructive jaundice and adequate hepatic, renal, and bone marrow function. Other exclusion criteria included stroke, history of bleeding, major surgical procedures performed within 28 days or minor procedures performed within 7 days prior to entry, brain metastases, cardiac disease (congestive heart failure, unstable angina, myocardial infarction within 6 months of enrollment, or arrhythmia), pregnancy, peripheral neuropathy, prior malignancy, or urine protein: creatinine (UPC) ratio greater than 1.0.

Statistical considerations

Our primary endpoint was the overall survival rate. Historical data suggest a 9-month survival duration for gemcitabine and oxaliplatin in patients with pancreatic cancer. Our objective was to determine if the triplet regimen would improve median survival by 5 months (i.e., to a 14 month median survival). Based on an expected accrual rate of 2.75 patients per month, we estimated that we would accrue a sample of 50 patients in 18 months with an additional 3 months of follow-up. The study was designed with a futility stopping rule such that if at any point in the study the probability of a 5-month improvement in median survival was less than 2.5%, the study would end.

Secondary endpoints included the objective response rate; time to progression; progression-free survival rate at 6, 9, and 12 months; and toxicity rate. Measurable lesions were defined as being greater than 20 mm when imaged using conventional computed tomography (CT) or magnetic resonance imaging or greater than 15 mm when measured using spiral CT. Lesions such as bone metastases, leptomeningeal disease, ascites, pleural and pericardial effusions, and lymphangitis were considered nonmeasurable. Radiologic response was evaluated using the Response Evaluation Criteria In Solid Tumors [13] for up to five target lesions per organ or 10 lesions per individual. A complete response (CR) was defined as disappearance of all target lesions. In addition to response and survival, toxic effects, hypertension, CA 19–9 level, and UPC ratio were assessed intermittently during treatment and at the conclusion of the study.

The Kaplan–Meier product-limit method [14] was used to generate survival curves, and the log-rank test was subsequently used to assess the difference in survival rate between patients with advanced tumors and those with metastatic tumors. In addition, a univariate Cox proportional hazards model [15] was used to assess the hazards ratios for survival. The Wilcoxon rank sum test was used to assess the association between continuous clinical factors and response, and Fisher's exact test was used to evaluate the effect of categorical clinical factors on response. The Spearman rank correlation coefficient method was used to assess the correlations among adverse events and the UPC

ratio. In the case of the CA 19–9 level and UPC ratio, both the numeric and logarithmic values were assessed for statistical significance.

Treatment

Treatment consisted of 10 mg/kg bevacizumab given on day 1 of each 2-week cycle. Premedication was allowed for patients experiencing allergic reactions to this agent. The initial dose was administered over 90 min with subsequent doses given over 30–60 min. Patients were specifically observed for hypertension, bleeding, and proteinuria (via regular urinalysis and UPC ratio). Toxicity was graded on the CTC version 3 scale [16]. Patients were removed from the study for grade 4 side effects of bevacizumab. Additionally, bevacizumab administration was discontinued for uncontrollable grade 3 or grade 4 hypertension, grade 3 hemorrhage if the patient was receiving anticoagulation medication, repeat hemorrhagic events, grade 4 venous thrombosis, arterial thrombosis of any grade, wound dehiscence, gastrointestinal perforation, or grade 4 nephrotic syndrome. Treatment with bevacizumab with anticoagulation therapy was permitted if a therapeutic INR was achieved without grade 3 or 4 hemorrhage and if no major blood vessels were involved by tumor. Gemcitabine was administered at 1,000 mg/m^2 via a fixed-dose-rate infusion of 10 mg/m^2/min (100 min) on day 1. Oxaliplatin was given at a dose of 100 mg/m^2 on day 2 over 2 h via a central catheter. This treatment was extended to 6 h for infusion reactions such as laryngopharyngeal dysesthesia.

Treatment with gemcitabine and oxaliplatin was delayed until the absolute neutrophil count was greater than 1,500/mm^3 and platelet count was greater than 100,000/mm^3. Patients were monitored during treatment for non-hematologic adverse events such as hypertension, bleeding, and proteinuria. Non-hematologic effects greater than grade 1 (except alopecia and neurotoxic effects) were cause for dose delay or reduction. Two dose reductions were allowed for each drug based on specific toxic effects.

Treatment was repeated every 2 weeks. Tumor restaging was performed every 6 weeks using CT. Responses were assessed locally without central review. CA 19–9 levels were also measured every 6 weeks. Concomitant therapy with other chemotherapeutics or investigational agents (such as antiemetics and antibiotics) was prohibited, although palliative and supportive care measures were allowed. Colony-stimulating factors were allowed.

Protocol treatment was discontinued because of disease progression, intercurrent illness, unacceptable toxic effects, dose delay for more than 28 days, grade 4 toxic effects as described above, voluntary withdrawal by the patient or investigator decision. Serious adverse events were reported to the U.S. Food and Drug Administration, the M.D. Anderson Institutional Review Board, and the study sponsor (Genentech, South San Francisco, CA).

Results

Patient population

Patient demographics are presented in Table 1. We enrolled a total of 51 patients, including 1 patient who withdrew from the study prior to any treatment. Their median age was 59 years (range 31–79 years). At enrollment, 14 patients had locally advanced disease, and the remainder had metastatic disease. Thirty-five patients were men. Most of the patients had an ECOG PS of 0 ($n = 11$) or 1 ($n = 34$). The median CA 19–9 level was 720 (range <1 [undetectable] to >70,000). Patients received treatment either at The University of Texas M. D. Anderson Cancer Center ($n = 35$) or The University of Oklahoma Health Sciences Center ($n = 15$).

Of the 50 patients, two patients had a prior pancreaticoduodenectomy, one of which had locally recurrent but unresectable disease while the other developed distant metastases. Two other patients had a prior distal pancreatectomy; one of whom had gross residual disease. They each developed metastatic disease for which they were enrolled. Seven patients had non-curative exploratory laparotomy for biopsy, cholecystectomy, or for aborted resection.

Survival

Kaplan–Meier analysis of overall survival is shown in Fig. 1. The median overall survival duration was

Table 1 Summary statistics of demographic data

Variable	Levels	Total	Variable	Levels	Total
Age	Median	59	Baseline Ca199	Median	720
	Range	31–79		Range	1–70,000
				NA	1 (2%)
Gender	Female	15 (30%)		≤500	22 (44%)
	Male	35 (70%)		>500	27 (54%)
Tumor	Advanced	14 (28%)	Baseline UPC	Median	1.23
	Metastasis	36 (72%)		Range	1–39
PS	NA	1 (2%)	Location	M.D. Anderson	35 (70%)
	0	11 (22%)		OHSC	15 (30%)
	1	34 (68%)			
	2	4 (8%)			

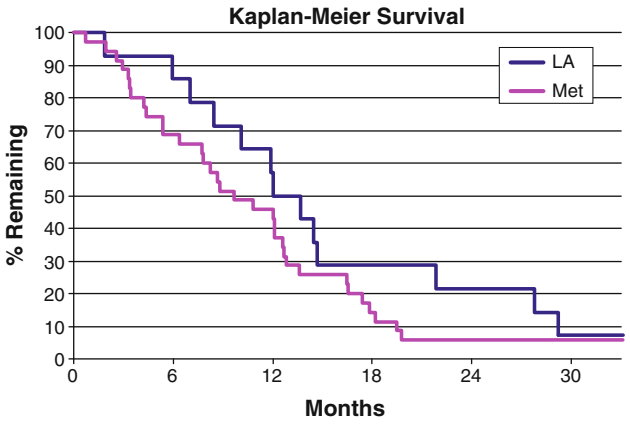

Fig. 1 Kaplan–Meier analysis of survival in patients with metastatic and locally advanced pancreatic cancer

11.9 months. The 6-month survival rate was 74%, and the 1-year survival rate was 42%. The survival rate at 18 months was 20%. Three patients with locally advanced disease terminated participation to undergo surgical resection with curative intent. One of these three was still alive at last follow-up. Survival among patients with locally advanced and metastatic disease was not different (12.8 vs. 10.2 months; $P = .33$).

In univariate analyses, baseline CA 19–9 correlated with survival, both when dichotomized at 500 IU/ml ($P = .004$, Table 2) and when included as a continuous $\log_2$-linear factor ($P = .004$). Specifically, a baseline CA 19–9 of >500 IU/ml carried a hazard ratio of 2.5 ($P = .004$, C.I. 1.33–4.66), and for every doubling of CA 19–9, there was an associated 15% increased risk of death (HR 1.15, $P = .004$, C.I. 1.05–1.27). The median survival duration in patients with low baseline CA 19–9 levels, defined as the bottom quintile for baseline CA 19–9 level (range 1–55), was 19.6 months. This was twice the median overall survival duration in patients in the top quintile for baseline CA 19–9 level (range 3,462–70,000), which was 8.2 months. The median survival duration in patients whose CA 19–9 level dropped at least 80% during treatment was 14.7 months, whereas that in patients whose CA 19–9 level dropped less than 80% was 8.1 months.

Patients with an objective response to treatment had a median survival better than those with stable disease or progression ($P = .007$), with median survivals of 15.6, 10.8, and 4.3 months, respectively. Non-assessable patients survived a median of 3.0 months. Patients with a PS of 0–1 had a survival of 12.0 months as compared to 4.8 among those with PS2, though this did not reach statistical significance. There was no discernable difference in survival based on baseline or change of UPC ratio.

Three patients with advanced disease underwent whipple surgery. Of these, two relapsed and died 15 and 22 months after enrollment; one has had long-term survival and is alive 37 months from start of treatment.

Post-protocol treatment was offered to at least 24 patients. This consisted of chemotherapy ($n = 17$), radiation ($n = 3$), both ($n = 3$), or RFA ($n = 1$). Of seven patients whose CA 19–9 had dropped by >50% during therapy and who started second line therapy, only one had a similar drop in CA 19–9 during second line therapy (of 78%). This patient received cpt-11 and docetaxel, which was associated with stable disease at the first restaging at 2 months but subsequent progression at 4 months. This patient survived 190 days on second line treatment, as compared to the other six patients whose survival ranged from 61 to 257 days.

Response

Forty-five patients were evaluable for response. The overall response rate was 36% (18 patients); in addition, 34% had stable disease (Table 3) for a total clinical benefit rate of 70%. In total, 17 of 25 (68%) patients with a decrease in CA 19–9 responded, while only 1 of 8 (12.5%) with a rise in CA 19–9 exhibited a radiologic response.

Using Wilcoxian and Fisher's exact test, a decrease in CA 19–9, height of UPC ratio, and development of systolic hypertension were each significantly associated with radiologic response (Table 4). Each of the 10 patients with the greatest increase in systolic blood pressure had a PR or SD. Conversely, of the ten patients with the least increase in systolic blood pressure, only 4 had such benefit.

Five patients were unavailable for response assessment. Two patients stopped treatment after one cycle for CVA and TIA. Three stopped during cycle two for CVA, gastric outlet obstruction, and GI perforation.

Three patients originally enrolled for locally advanced disease were ultimately able to attempt surgery. Patient #2 had an R0 resection with post-op gem/ox/bevacizumab for 6 months after therapy. The patient relapsed 7 months after surgery, and received salvage chemotherapy and radiation. Death came approximately 16 months after surgery.

Patient #7 had an excellent PR to Gem/Ox/bev and underwent an R0 resection with 10 lymph nodes negative. He has been followed with surveillance and currently remains alive.

Patient #9 had surgery 7 months after beginning chemo. This was complicated by a prolonged hospitalization for sepsis. Relapse occurred 5 months after surgery and the patient died shortly thereafter.

Toxicity

The overall grade 3–4 toxicity rate was 94%. The most frequent grade 3–4 event was fatigue (44%) followed

Table 2 Univariate Cox proportional hazards model to assess the association between clinical factors and overall survival

Variable	*N*	Estimate	SE	*P*	HR	95% CI of HR	
Age	50	0.015	0.013	0.252	1.015	0.989	1.042
Gender (male vs. female)	50	0.166	0.319	0.604	1.18	0.631	2.206
Tumor (met vs. advanced)	50	0.323	0.329	0.325	1.382	0.726	2.631
PS (12 vs. 0)	49	0.609	0.377	0.106	1.838	0.879	3.845
Log2 (baseline ca199)	49	0.144	0.05	0.004	1.154	1.047	1.273
Baseline Ca199 (≥500 vs. <500)	49	0.913	0.319	0.004	2.492	1.334	4.656
Delta Ca199(decrease vs increase)	34	0.017	0.413	0.968	1.017	0.452	2.285
Delta Ca199 (<50% decrease vs. increase)	34	0.476	0.533	0.371	1.610	0.567	4.572
(≥50% decrease vs increase)		−0.116	0.433	0.789	0.891	0.381	2.081
Log2 (baseline UPC)	48	0.204	0.163	0.21	1.227	0.891	1.688
UPC ratio (highest/baseline)	44	−0.01	0.022	0.641	0.99	0.948	1.033
Delta UPC (<50% increase vs. no change)	45	0.155	0.412	0.706	1.168	0.521	2.617
(≥50% increase vs. no change)		−0.091	0.383	0.813	0.913	0.431	1.935
Abdominal pain (≥G3 vs. others)	50	0.486	0.34	0.153	1.626	0.834	3.168
Cold intolerance (≥G3 vs. others)	50	−0.176	0.44	0.689	0.839	0.354	1.987
Shortness breath (≥G3 vs. others)	50	−0.194	0.319	0.543	0.824	0.441	1.538
Neuro sx (≥G3 vs. others)	50	−0.369	0.475	0.437	0.691	0.272	1.754
Hypertension (≥G3 vs. others)	50	−0.696	0.415	0.094	0.499	0.221	1.125
Response (CR + PR vs. SD PD)	45	−0.859	0.321	0.007	0.424	0.226	0.795

Table 3 Treatment effectiveness—entire population

Outcome		Result
Median survival		12.0 months
1-Year survival		21 (42%)
18-Month survival		10 (20%)
2-Year survival		5 (10%)
Response	# (Pct)	Median O.S. (C.I.)
Partial response	7 (14%)	15.6 (12.0–19.5)
Stable disease	28 (56%)	10.8 (8.2–12.6)
Progressive Dz	10 (20%)	4.3 (3.4–5.3)
Not assessable	5 (10%)	3.0 (0.8–5.0)

by nausea (38%), shortness of breath (32%), neuropathy (26%), abdominal pain (26%), constipation (20%), neutropenia (18%), hypertension (14%), headache (10%), and vomiting (10%). There were two fatal events during the study, including one episode of GI perforation, and one CVA; the patient died shortly thereafter. There was also one non-fatal CVA and one patient with a TIA. There was one instance of grade 3 proteinuria.

Cold intolerance was significantly and negatively associated with UPC ratio ($P = .023$), whereas proteinuria and hypertension were positively associated with UPC ratio ($P = .0019$ and .0025, respectively).

Discussion

Treatment of pancreatic cancer with the combination of oxaliplatin, bevacizumab, and gemcitabine resulted in a median overall survival duration twice that produced by treatment with single-agent gemcitabine as reported by Burris and colleagues in 1997 [2] (11.9 months versus 5.4 months). We note that the proportion of patients with locally advanced disease in our trial was virtually identical to that reported for the Burris trial. However, when the results of treatment with GEMOX plus bevacizumab are viewed in the context of other recently reported findings, they provide insight into the challenges of clinical investigation of pancreatic cancer. The ECOG recently reported on a three-arm phase III trial that compared standard-dose gemcitabine given over 30 min, a higher dose of gemcitabine (1,500 mg/m^2) given at a fixed-dose-rate of 10 mg/m^2/min, and GEMOX [11]. The results showed that both fixed-dose-rate gemcitabine and GEMOX were perhaps slightly superior to standard-dose gemcitabine in terms of response rate, median survival duration, and 1 year survival rate, but none of these differences were statistically significant.

Since the initiation of our trial, both a Cancer and Leukemia Group B study comparing gemcitabine plus placebo with gemcitabine plus bevacizumab [17] and the AVITA trial [18] comparing gemcitabine and erlotinib plus a placebo with gemcitabine and erlotinib plus bevacizumab showed no survival benefit in patients with advanced

Table 4 Wilcoxon rank sum test or Fisher's exact test to assess the association between clinical factors and overall response (CR ± PR)

Variable	Levels	Response (CR ± PR)		*P*
		No 29 (61.7%)	Yes 18 (38.3%)	
Age	Mean (SD)	57.9 (8.9)	58.4 (10)	0.78
	Median (min, max)	59 (40, 77)	59.5 (31, 79)	
Gender	Female	7 (50%)	7 (50%)	0.512
	Male	20 (64.5%)	11 (35.5%)	
Tumor	Advanced	7 (58.3%)	5 (41.7%)	1
	Metastasis	20 (60.6%)	13 (39.4%)	
PS	0	6 (54.5%)	5 (45.5%)	0.738
	1 or 2	20 (60.6%)	13 (39.4%)	
Log2 (baseline CA199)	Mean (SD)	9.6 (3.5)	7.9 (3.7)	0.12
	Median (min, max)	9.9 (1.4, 15.8)	8.6 (0, 13.1)	
Baseline CA199	<500	9 (47.4%)	10 (52.6%)	0.222
	≥500	17 (68%)	8 (32%)	
Delta Ca199	Increase	7 (87.5%)	1 (12.5%)	0.019
	<50% decrease	3 (42.9%)	4 (57.1%)	
	≥50% decrease	5 (27.8%)	13 (72.2%)	
Delta Ca199	Increase	7 (87.5%)	1 (12.5%)	0.012
	Decrease	8 (32%)	17 (68%)	
Log2 (baseline UPC)	Mean (SD)	−2.8 (0.9)	−3.1 (0.7)	0.31
	Median (min, max)	−3.1 (−4.6, −0.8)	−3.3 (−4.3, −1.3)	
UPC ratio (highest/baseline)	Mean (SD)	2.4 (2.8)	7.7 (11.6)	0.047
	Median (min, max)	1.3 (1, 13)	2.6 (1, 45.9)	
Delta UPC	No change	8 (72.7%)	3 (27.3%)	0.086
	<50% increase	9 (75%)	3 (25%)	
	≥50% increase	8 (40%)	12 (60%)	
Abdominal pain	<G3	19 (55.9%)	15 (44.1%)	0.482
	≥G3	8 (72.7%)	3 (27.3%)	
Cold intolerance	<G3	23 (59%)	16 (41%)	1
	≥G3	4 (66.7%)	2 (33.3%)	
Shortness breath	<G3	21 (65.6%)	11 (34.4%)	0.317
	≥G3	6 (46.2%)	7 (53.8%)	
Neuro sx	<G3	23 (59%)	16 (41%)	1
	≥G3	4 (66.7%)	2 (33.3%)	
Hypertension	<G3	26 (68.4%)	12 (31.6%)	0.012
	≥G3	1 (14.3%)	6 (85.7%)	

pancreatic cancer who were randomized to receive bevacizumab.

If oxaliplatin does not add a significant survival benefit to gemcitabine and if bevacizumab likewise adds no benefit, one might assume that the three-drug combination of GEMOX plus bevacizumab offers no meaningful survival advantage over single-agent gemcitabine. In fact, relative to other published studies, our median survival was fairly long. It therefore remains conceivable that the interaction of the three drugs has an effect that we did not observe in this single-arm trial. However, more concrete evidence of efficacy has been demonstrated in the recently described FOLFIRINOX regimen, which demonstrated improved response rate and progression-free survival, and overall survival [19]. This finding may suggest a better drug interaction between fluorouracil and oxaliplatin as compared with gemcitabine. It may also reflect a role for irinotecan in the treatment of pancreatic cancer. However, there was also considerable toxicity among the FOLFIRINOX-treated patients, often with doubling or tripling of grade 3–4 toxicity rates as compared with gemcitabine.

Survival in our study was similar to that of the GTX regimen, which demonstrated a median survival of 11.2 months in metastatic patients [20] in a retrospective

analysis. Formal comparisons are difficult, however, as no formal phase II or III studies of GTX have been published.

Nevertheless, our findings offer important lessons. First, GEMOX plus bevacizumab did not meet the primary goal of a 14 month overall survival; thus, we have no plans to study this combination in a larger randomized trial. Second, PS remains a strong predictor of survival no matter the treatment. A pooled analysis of cytotoxic gemcitabine doublets (gemcitabine plus drug X) suggested that patients with good PS experience statistically significant survival benefits with the addition of a platinum analog or a fluorinated pyrimidine [21]. Given this result, our patients may have benefited from GEMOX beyond that expected using gemcitabine alone, as 90% of our enrolled patients had an ECOG PS of zero or one.

In addition, enrollment of a mixed population of patients (those with locally advanced disease and those with metastatic disease) makes comparison of our findings with those of similar trials more challenging. For example, investigators at the University of California, San Francisco previously reported on the combination of fixed-dose-rate gemcitabine with cisplatin and bevacizumab, limiting patient eligibility to those with metastatic disease. Their median survival duration was 8.2 months [22]. Similarly, the ECOG study reported by Poplin and colleagues had only 10% patients with locally advanced disease and a median survival of 9 months [11]. Our median survival appears longer at 11.9 months, but 28% of our patients had locally advanced disease. Furthermore, patients enrolled in our trial received treatment at two large tertiary care hospitals with experience in the overall management of patients with advanced pancreatic cancer and in conducting clinical trials. Therefore, patient selection and sophisticated supportive care measures may also partially explain the survival results irrespective of the regimen delivered.

Our observation of longer survival durations in patients with low CA 19–9 levels than in those with high levels is in accordance with previously published results, [23] although our relatively small number of patients limited this analysis. Likewise, our observation of improved survival durations with >80% decline in CA 19–9 is in accordance with previous observations.

That bevacizumab use is associated with hypertension is not a new finding. However, our observation that the presence of hypertension correlates with response to treatment adds to a small but growing body of literature supporting this assertion. Friberg et al. [24] reported a median survival of 13.7 months in 6 patients with early hypertension after receiving treatment of pancreatic cancer with gemcitabine and bevacizumab as opposed to 8.7 months in 40 patients without such hypertension. Although this result was not significant ($P = .067$), the small size of the study population likely contributed to the lack of statistical significance. Similarly, Bono et al. [25] showed that patients with renal cancer undergoing treatment with bevacizumab had longer median disease-free survival durations if they required antihypertensive therapy than if they did not (8.1 vs. 4.2 months; $P = .036$).

Our regimen proved to be difficult to tolerate. Nausea, fatigue, and neuropathy were among the most common grade 3 and 4 toxic effects. In all, 47 patients experienced grade 3 or 4 toxic effects. Because many of these effects (e.g., constipation) may have been caused by the underlying disease or supportive measures (e.g., use of narcotics), determining how much this toxicity is attributable to the chemotherapy itself is somewhat difficult.

In conclusion, in this phase II study, the combination of GEMOX and bevacizumab resulted in one of the highest response rates and longest survival durations observed in studies of advanced pancreatic cancer. It did not meet our prespecified median survival goal of 14 months. We also observed a moderate amount of toxicity, with many patients experiencing grade III/IV side effects. Accordingly, although our median overall survival duration of 11.9 months appears to be encouraging, we do not plan further investigation of this regimen. Randomized phase II trials in which enrollment is limited to patients with metastatic pancreatic cancer and good PS may be the preferred method of efficiently selecting therapies that may ultimately demonstrate survival superior to current standards.

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References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59:225–249
2. Louvet C, LaBianca R, Hammel P et al (2005) Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic patients with pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 23:3509–3516
3. Burris HA, Moore MJ, Andersen J et al (1997) Improvements in survival and clinical benefit with gemcitabine for advanced pancreatic cancer: a randomized trial. J Clin Oncol 15:2403–2413
4. Heinemann V, Quietzsch D, Gieseler F et al (2006) Randomized Phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 24:3946–3952
5. Rocha Lima CM, Green MR, Rotche R et al (2004) Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 18:3776–3783
6. Oettle H, Richards D, Ramanathan RK et al (2005) A Phase III trial of pemetrexed plus gemcitabine versus gemcitabine in

patients with unrespectable or metastatic pancreatic cancer. Ann Oncol 16:1639–1645
7. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB (2002) Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: eastern cooperative oncology group trial E2297. J Clin Oncol 20:3270–3275
8. Cunningham D, Chau I, Stocken D et al (2009) Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 27:5513–5518
9. Moore MJ, Goldstein D, Hamm J et al (2007) Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the national cancer institute of Canada clinical trials group. J Clin Oncol 25:1960–1966
10. Faivre S, Chan D, Salinas R, Woynarowska B, Woynarowski JM (2003) DNA strand breaks and apoptosis induced by oxaliplatin in cancer cells. Biochem Pharmacol 66:225–237
11. Poplin E, Feng Y, Berlin J et al (2009) Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30 min infusion) in patients with pancreatic carcinoma E7201: a trial of the eastern cooperative oncology group. J Clin Oncol 27:3778–3785
12. Kindler HL, Friberg G, Singh DA et al (2005) Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol 23:8033–8040
13. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Nat Cancer Inst 92:205–216
14. Kaplan EL, Meier P (1958) Non parametric estimation from incomplete observations. J Am Stat Assoc 53:457–481
15. Cox DR (1972) Regression models and life tables. J R Stat Soc A 29:187–220
16. Available at: http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm
17. Kindler HL, Niedzwiecki D, Hollis D et al (2007) A double-blind, placebo controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): a preliminary analysis of cancer and leukemia group B (CALGB) 80303. J Clin Oncol 25:18s (suppl; abstr 4508)
18. Van Cutsem E, Vervenne WL, Bennouna J et al (2009) Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 27:2231–2237
19. Conroy T, Desseigne F, Ychou M et al (2010) Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial. J Clin Oncol 28:15s (suppl, Abstr 4010)
20. Fine RL, Fogelman DR, Schreibman SM, Desai M, Sherman W, Strauss J, Guba S, Andrade R, Chabot J (2008) The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. Cancer Chemother Pharmacol 61(1):165–167
21. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C (2008) Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer 8:82
22. Ko AH, Dito E, Schillinger B et al (2008) A phase II study evaluating bevacizumab in combination with fixed-dose gemcitabine and low-dose cisplatin for metastatic pancreatic cancer: is an anti-VEGF strategy still applicable? Invest New Drugs 26(5):463–471
23. Ko AH, Hwang J, Venook AP, Abbruzzese JL, Bergsland EK, Tempero MA (2005) Serum CA 19–9 response as a surrogate for clinical outcome in patients receiving fixed-dose rate gemcitabine for advanced pancreatic cancer. Br J Cancer 93:195–199
24. Friberg G, Kasza K, Vokes E, Kindler H (2005) Early Hypertension as a potential pharmacodynamic (PD) marker for survival in pancreatic cancer (PC) patients (pts) treated with bevacizumab (B) and gemcitabine (G). J Clin Oncol 23(16S):3020
25. Bono P, Elfving H, Utriainen T et al (2009) Letter to the editor. Annal Oncol 20:393–394