VEGF remains an interesting target in advanced pancreas cancer (APCA): results of a multi-institutional phase II study of bevacizumab, gemcitabine, and infusional 5-fluorouracil in patients with APCA

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Background: We investigated the safety and efficacy of bevacizumab combined with gemcitabine followed by infusional 5-fluorouracil (5-FU) in patients with advanced pancreas cancer (APCA).

Design: Patients with untreated APCA received bevacizumab 10 mg/kg, gemcitabine 1000 mg/m^2 over 100 min, and 5-FU 2400 mg/m^2 over 48 h on days 1 and 15 of each 28-day cycle. The primary end point was the proportion of patients with progression-free survival (PFS) at 6 months from initiation of therapy. If PFS at 6 months was ≥41%, the regimen would be considered promising.

Results: Forty-two patients were enrolled in the study; of which, 39 were evaluable for primary end point. PFS at 6 months was 49% (95% CI 34% to 64%). Median PFS was 5.9 months (95% CI 3.5 to 8.1) and median overall survival (OS) was 7.4 months (95% CI 4.7 to 11.2). Partial response and stable disease occurred in 30% and 45% of patients, respectively. Treatment-related hypertension and normal baseline albumin correlated with an improved response rate, PFS and OS. Grade 3 to 4 toxicities included fatigue (14%), hypertension (5%), and venous thrombosis (5%).

Conclusions: The study met its primary end point. Further investigation of anti-VEGF therapy in combination with fluoropyrimidine-based therapy is warranted in APCA. Treatment-related hypertension and normal baseline albumin may predict for the efficacy of bevacizumab and should be investigated in prospective studies.

Key words: bevacizumab, 5-fluorouracil, gemcitabine, pancreas cancer, VEGF

introduction

Pancreas cancer (PCA) is the fourth leading cause of cancer death in the United States [1]. Prognosis remains dismal, with a 5-year survival of <5% for all stages [2]. Surgical resection followed by adjuvant therapy offers the only chance for cure; however, <15% of patients present with resectable disease [3]. Cytotoxic chemotherapy with gemcitabine has been the standard of care and the backbone of experimental regimens in advanced pancreas cancer (APCA) for over a decade based on a modest clinical benefit over bolus 5-fluorouracil (5-FU) [4]. Since the late 1990s, minimal progress has been made to improve survival for these patients with gemcitabine-based combination regimens [5–12]. Recently published phase III data show a significant survival benefit for the combination of 5-FU, oxaliplatin, and irinotecan (FOLFIRINOX) over gemcitabine in patients with untreated metastatic pancreas cancer [13]; however, because of the significant toxicity associated with FOLFIRINOX, the regimen is only appropriate for a select subset of patients. The chemoresistance of pancreas cancer has led to a continuing search for new therapeutic targets.

Vascular endothelial growth factor (VEGF) is a pro-angiogenic growth factor implicated in the pathogenesis of many cancers [14, 15]. In PCA, VEGF promotes tumor growth, invasion, and metastases via activation of the MAPK pathway [16], and also functions as an autocrine growth factor for PCA cells [17, 18]. Overexpression of VEGF and its receptors occurs in >90% of PCA and correlates with poor prognosis [19–23]. Preclinical data suggest that inhibition of VEGF attenuates PCA growth and metastasis [24–26]. Thus, VEGF represents an attractive therapeutic target in human PCA.

Bevacizumab (Avastin®, Roche/Genentech, Inc., South San Francisco, USA) is a recombinant humanized monoclonal

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antibody that binds VEGF-A, blocking its interaction with its receptors. Bevacizumab improves outcomes in combination with chemotherapy in a number of advanced malignancies [27–32], however, its role in APCA remains controversial, and current recommendations for its use do not extend outside the investigational setting [33]. Preclinical data and promising results from early clinical studies [24, 25, 34–36] suggested investigation of antiangiogenic therapies in APCA. While phase III studies adding bevacizumab to gemcitabine [37] or gemcitabine and erlotinib [38] failed to confirm an overall survival (OS) benefit in APCA, bevacizumab improved PFS when added to gemcitabine and erlotinib [38]. Correlative work from this trial [39] suggested that pretreatment plasma levels of VEGFA and VEGFR2 may emerge as important predictive biomarkers to identify patients who are most likely to benefit from antiangiogenic therapy. These data suggest that VEGF may remain a valid target in appropriately selected patients with APCA.

Preliminary clinical evidence suggested that gemcitabine given at a fixed dose rate (FDR) of 10 mg/m^2/min had an advantage over standard gemcitabine in patients with APCA [40]. The results of a follow-up three-arm phase III trial reported only a trend toward a survival benefit for FDR gemcitabine over standard gemcitabine, however that study was possibly underpowered [11]. 5-FU has single-agent activity in PCA [41] and phase III data suggest that 5-FU and gemcitabine are equivalent in the adjuvant setting [42]. Of greater interest, gemcitabine has been shown to act as a potential biomodulator of 5-FU activity [43]. Preclinical studies confirm that the sequential administration of prolonged infusion of gemcitabine followed by 5-FU exposure for 24 h results in significant synergistic antitumor activity in cancer cell lines [44]. In early clinical trials of patients with advanced gastrointestinal and genitourinary cancers [45, 46], the combination of prolonged-infusion gemcitabine followed by a fluoropyrimidine showed promising clinical activity. Finally, 5-FU has known clinical synergy with bevacizumab in colon cancer [29–31, 48] and administration of 5-FU as a continuous infusion improves survival and response rate over bolus administration [48].

Based on these observations, we designed a phase II study to investigate the efficacy and safety of the combination of bevacizumab combined with FDR gemcitabine followed by infusional 5-FU over 48 h in patients with untreated APCA.

patients and methods

patient eligibility

Eligible patients were required to have biopsy-proven stage III or IV pancreatic adenocarcinoma with measurable disease by RECIST 1.0 [50], Eastern Cooperative Oncology Group (ECOG) performance status 0–1, no prior treatment for metastatic disease, and adequate bone marrow (neutrophils >1500/μl, hemoglobin >9 g/dl, platelets >100 000/μl), kidney [creatinine < 1.5 × upper limit of normal (ULN)], and liver (bilirubin ≤ ULN, AST/ALT ≤ 1.5 × ULN or ≤ 3 × ULN with liver metastases) function. Prior adjuvant chemotherapy (including gemcitabine) was allowed, provided that >4 weeks had elapsed since the end of therapy. Exclusion criteria included prior treatment with VEGF inhibitors, brain metastases, congestive heart failure requiring active therapy, myocardial infarction or

stroke within the past 6 months, bleeding diathesis, uncontrolled hypertension or diabetes mellitus, and proteinuria. All patients provided written informed consent before study enrollment.

treatment plan

This was a multicenter phase II study including the Ohio State University and University of Michigan. Patients received bevacizumab followed by gemcitabine then 5-FU on days 1 and 15 of each 28-day cycle. Bevacizumab was administered intravenously at a dose of 10 mg/kg over 30 min. Gemcitabine was administered intravenously at a dose of 1000 mg/m^2 over 100 min (FDR, 10 mg/m^2/min). 5-FU was given as a continuous 48-h intravenous infusion at a dose of 2400 mg/m^2. Treatment was continued until disease progression, intolerable toxicity, intercurrent illness or death preventing further treatment, or patient withdrawal of consent.

dose delays and modifications

Patients were required to have neutrophils ≥1500/μl, platelets ≥100 000/μl, and all other treatment-related toxicity resolved to grade ≤1 in order to begin a treatment cycle. Dose reductions of gemcitabine were corrected to preserve the FDR. Gemcitabine was reduced to 75% of the original dose for grade 3 or 4 thrombocytopenia, febrile neutropenia (grade 4 neutropenia and ≥grade 2 fever), and grade 3 or 4 nonhematologic toxicity, excluding nausea and vomiting controlled with supportive measures. 5-FU was reduced to 75% of the original dose for febrile neutropenia, grade 3 palmar-plantar erythrodysesthesia (hand and foot syndrome), and any grade 3 or 4 nonhematologic toxicity, excluding nausea and vomiting controlled with supportive measures. There were no recommended dose reductions for bevacizumab. If adverse events occurred that required bevacizumab to be held, the dose remained the same once treatment resumed. Bevacizumab was discontinued and patients were removed from study for grade IV hypertension, venous thrombosis, or hemorrhage, arterial thrombosis of any grade, gastrointestinal perforation, wound dehiscence requiring medical or surgical intervention, recurrent toxicities despite dose modifications, or any toxicity felt by the investigator to prohibit safe continuation of therapy.

assessment of toxicity and response

Adverse events were graded according to the NCI-CTCAE v 3.0. Pretreatment assessment included baseline history and physical, complete blood count, serum chemistry including liver functions, urine protein/ creatinine ratio, serum βhCG, EKG, and CA 19-9 level. These assessments (excluding EKG) were repeated on day 1 of each subsequent cycle along with toxicity assessment. On day 15 of every cycle, patients had physical examination, toxicity assessment, complete blood count, and serum chemistries. Radiographic assessment of response was carried out at baseline and every 8 weeks using the same imaging modality [computed tomography (CT) or magnetic resonance imaging (MRI)] used to establish baseline tumor measurements. Responses were measured according to RECIST 1.0 [49]. Hypertension was assessed by blood pressure measurement on days 1 and 15 of each cycle. Baseline albumin was measured before initiation of treatment, and subsequent measurements were obtained on days 1 and 15 of each treatment cycle.

statistical methods

The primary end point was the percentage of patients free from disease progression or death at 6 months (24 weeks) from initiation of therapy. Secondary endpoints include overall response rate (ORR) as defined by RECIST 1.0 [49], 6-month and 1-year survival rates, OS, and the frequency and severity of treatment-associated adverse events. Using a Fleming

single-stage phase II study design, we planned to enroll 39 evaluable patients to determine whether the true 24-week PFS rate was 0.30 or less versus 0.50 or more [$\alpha = 0.10$; $\beta = 0.10$]. Patients were considered nonevaluable for the primary end point if they died from nontreatment related or nondisease related cause before the 6-month assessment period, or if they were removed from the study for treatment-related toxicity with <6 months of follow-up. If at least 16 evaluable patients (41%) were progression-free at 6 months, the regimen will be recommended for further study. *Post hoc* subgroup analyses included patients with and without treatment-related hypertension of any CTCAE grade, and patients with normal ($\geq$3.4 g/dl) and low (<3.4 g/dl) baseline albumin. OS, PFS, and ORR were compared between the subgroups. Survival curves were estimated using the Kaplan–Meier method, and 95% confidence intervals for the medians were provided. The group difference in survival was assessed with the log-rank test. Response rates were compared using Fisher's exact test. For all but the primary endpoints, data were analyzed based on the intention-to-treat principle.

results

patient characteristics (Table 1)

Patient characteristics are detailed in Table 1. Forty-two patients (23 F, 19 M) with a median age 60 (range 36 to 79)

Table 1. Patient characteristics (N = 42)

Characteristic	N (%)
Sex	
Male	19 (45)
Female	23 (55)
Age (years)	
Median	60
Range	36 to 79
Race/ethnicity	
Caucasian	37 (88)
African American	3 (7)
Other	2 (5)
ECOG performance status	
0	15 (36)
1	27 (64)
Prior adjuvant therapy	2 (5)
Gemcitabine-based[a]	1 (50)
Chemoradiation[b]	1 (50)
Disease stage	
III	2 (5)
IV	40 (95)
Site of metastasis (N = 40)	
Liver only	29 (73)
Liver + other	2 (5)
Other only	9 (23)
CA19-9	
Normal (≤37 U/ml)	6 (14)
Elevated (>37 U/ml)	36 (86)
Albumin	
Normal (≥3.4 g/dl)	28 (67)
Low (<3.4 g/dl)	14 (33)

[a]Patients developed recurrence/metastases while on a clinical trial of gemcitabine ± *Saccharomyces cerevisiae* vaccine.
[b]Patients were treated on a clinical trial of 5-FU, cisplatin, interferon-α, and radiation.

and ECOG performance status of zero or one were enrolled between January 2007 and October 2008. Two patients (5%) had stage III disease and 40 patients (95%) had stage IV disease. The most common site of metastatic disease was the liver (75%). Two patients had recurrent metastatic disease after prior surgical resection and adjuvant therapy. Most patients (86%) had elevated baseline CA19-9 levels (>37 U/ml). Sixty-seven percent of patients had normal baseline albumin (≥3.4 g/dl) and 33% of patients had low albumin (<3.4 g/dl) before initiation of treatment.

Of the 42 patients enrolled, 39 were evaluable for the primary end point. Two patients were removed as pre-specified from study, before reaching the 6-month assessment point, due to treatment-related toxicity. Of note, both these patients had stable disease and CA19-9 declines of >25% at the time of removal from study. The third patient was removed from study due to noncompliance unrelated to toxicity. Forty patients were assessable for response. All 42 patients were evaluable for survival and toxicity analyses.

toxicity (Table 2)

Toxic effects are outlined in Table 2. The most frequent treatment-related toxicities were vomiting (69%), anemia (66%), fatigue (61%), and nausea (59%). Chemotherapy-related grade 3–4 toxicities were uncommon and included fatigue (14%), vomiting (5%), lymphopenia (5%), nausea (2%), anemia (2%), thrombocytopenia (2%), and ALT elevation (2%). Grade 3 toxicities attributed to bevacizumab were rare and included

Table 2. Toxic effects observed according to the National Cancer Institute Common Toxicity Criteria Version 3.0[a] (N = 42)

	Grade 1, N (%)	Grade 2, N (%)	Grade 3, N (%)	Grade IV, N (%)
Hematologic				
Anemia	19 (45)	8 (19)	0 (0)	1 (2)
Thrombocytopenia	11 (26)	1 (2)	1 (2)	0 (0)
Leukopenia	8 (19)	3 (7)	0 (0)	0 (0)
Neutropenia	4 (10)	2 (5)	0 (0)	0 (0)
Lymphopenia	4 (10)	2 (5)	2 (5)	0 (0)
Non-hematologic				
Fatigue	6 (14)	14 (33)	6 (14)	0 (0)
Vomiting	23 (55)	8 (19)	2 (5)	0 (0)
Nausea	19 (45)	5 (12)	1 (2)	0 (0)
Diarrhea	13 (33)	3 (7)	0 (0)	0 (0)
Elevated ALT	5 (12)	1 (2)	1 (2)	0 (0)
Elevated AST	6 (14)	0 (0)	0 (0)	0 (0)
Mucositis	6 (14)	3 (7)	0 (0)	0 (0)
Altered sense of taste	11 (26)	1 (2)	0 (0)	0 (0)
Hypertension	5 (12)	1 (2)	2 (5)	0 (0)
Fistula formation	0 (0)	0 (0)	1 (2)	0 (0)
Proteinuria	3 (7)	1 (2)	0 (0)	0 (0)
Bleeding	4 (10)	2 (5)	1 (2)	0 (0)
Thrombosis	0 (0)	0 (0)	2 (5)	0 (0)
Headache	5 (12)	0 (0)	0 (0)	0 (0)
Rash	2 (5)	3 (7)	0 (0)	0 (0)
Peripheral sensory neuropathy	5 (12)	1 (2)	0 (0)	0 (0)

[a]Maximum grade per patient.

venous thrombotic events (5%), hypertension (5%), epistaxis (2%), and fistula formation (2%). Only one patient experienced grade 4 toxicity (anemia) and there were no treatment-related deaths. Hypertension was observed in eight patients (19%). Fifteen patients (38%) required treatment delay or dose reduction. Bevacizumab was discontinued in one patient due to progressive renal insufficiency and treatment-related grade 2 proteinuria (urine protein:creatinine ratio 3.4) in the setting of underlying chronic renal insufficiency. Three patients were removed from the study as pre-specified due to treatment-related toxicity including grade 3 venous thrombosis ($n = 2$) and persistent grade 2 thrombocytopenia ($n = 1$).

efficacy (Table 3 and Figure 1A)

Treatment efficacy data are summarized in Table 3. Final data analysis is conducted 4 years from enrollment of the first patient. At the time of the final analysis, 3 patients are still alive and 39 patients have died. Freedom from progression is demonstrated in 19 of 39 patients (49%) at 24 weeks (95% CI 34–64%); therefore, the primary end point of the study is met. Partial response (PR) and stable disease (SD) are seen in 30% and 45% of patients, respectively, with a disease control rate (PR + SD) of 75%. Kaplan–Meier survival curves are provided in Figure 1. Median PFS is 5.9 months (95% CI 3.5 to 8.1) and median OS is 7.4 months (95% CI 4.7 to 11.2). Six-month and 1-year survival were 60 and 36%, respectively. Thirty-six patients (86%) had elevated CA 19-9 levels before therapy. Fifty-nine percent of those patients experienced >25% maximum reduction of CA 19-9 levels, and 54% experienced >50% reduction.

potential predictors of clinical outcome (Table 3 and Figure 1B and C)

Data regarding the relationship between hypertension ($N = 8$), baseline albumin levels and clinical outcomes (ORR, PFS, and OS) are presented in Table 3. Patients with treatment-related hypertension had significantly improved ORR (63 versus 22%; $P = 0.0386$), and mOS (12 versus 6.1 months, $P = 0.0166$) and improved PFS (7.6 versus 4.9 months, $P = 0.38$) that did not reach statistical significance, compared with patients who did not experience treatment-related hypertension. Patients with normal baseline albumin (≥ 3.4 g/dl, $N = 28$) at study entry had trend toward improvement in ORR (36 versus 17%, $P = 0.2848$), and significantly prolonged mPFS (7.7 versus 2.7 months, $P = 0.0124$) and mOS (11.7 versus 3.2 months, $P = 0.0017$) compared with patients with low baseline albumin (<3.4 g/dl, $N = 14$) (Figure 1B and C).

discussion

The prognosis of PCA remains poor with little progress made in the last few decades. In the last decade, phase III studies of gemcitabine in combination with other cytotoxics have yielded no improvement in survival [5–9, 11, 50–53]. This has led to investigation of biologic targets including anti-VEGF therapy.

We evaluated a rational combination of bevacizumab combined with FDR gemcitabine followed by infusional 5-FU in PCA. The choice of the combination and its schedule

focuses on the biomodulation of infusional 5-FU by a prolonged infusion of gemcitabine and the known synergism between 5-FU and bevacizumab [29–31, 47]. In our study, we observed interesting clinical efficacy and reached the primary study end point with 49% of patients being free of disease progression at 24 weeks. The combination was well tolerated with expected and manageable toxicity. Our observed objective response rate, 1-year survival, OS and progression-free survival (PFS) are interesting compared with historical controls in advanced PCA [5–12, 36–38, 50–55]. Confirming the observed

Table 3. Treatment efficacy

Endpoint	N (%)
PFS at 6 months[a]	19 (49) (95% CI 34 to 64)
Response[b]	
CR	0 (0)
PR	12 (30)
SD	18 (45)
PD	10 (25)
Albumin[c] ≥ 3.4 g/dl	10 (36)[d]
Albumin <3.4 g/dl	2 (17)[e]
P-value	0.2848
Hypertension[f]	5 (63)[g]
No hypertension	7 (22)[h]
P-value	0.0386
CA 19-9 maximum reduction[i]	
>25%	23 (59)
>50%	21 (54)
Median PFS (months)[j]	5.9 (95% CI 3.5–8.1)
Albumin[e] ≥ 3.4 g/dl	7.7
Albumin <3.4 g/dl	2.7
P-value	0.0124
Hypertension[f]	7.6
No hypertension	4.9
P-value	0.38
Median OS (months)[j]	7.4 (95% CI 4.7–11.2)
Albumin[e] ≥ 3.4 g/dl	11.7
Albumin <3.4 g/dl	3.2
P-value	0.0017
Hypertension[f]	12
No hypertension	6
P-value	0.0166
6-month survival[j]	60%
1-year survival[j]	36%

[a]39 patients were considered evaluable.
[b]40 patients were considered evaluable.
[c]Baseline albumin before treatment.
[d]Objective response rate based on 28 evaluable patients with albumin ≥ 3.4 g/dl.
[e]Objective response rate based on 12 patients with albumin <3.4 g/dl.
[f]Grade ≥ 1 treatment-related hypertension as defined and graded according to CTCAE v 3.0.
[g]Objective response rate based on eight evaluable patients with hypertension.
[h]Objective response rate based on 32 evaluable patients without hypertension.
[i]36 patients (86%) had baseline elevated CA 19-9.
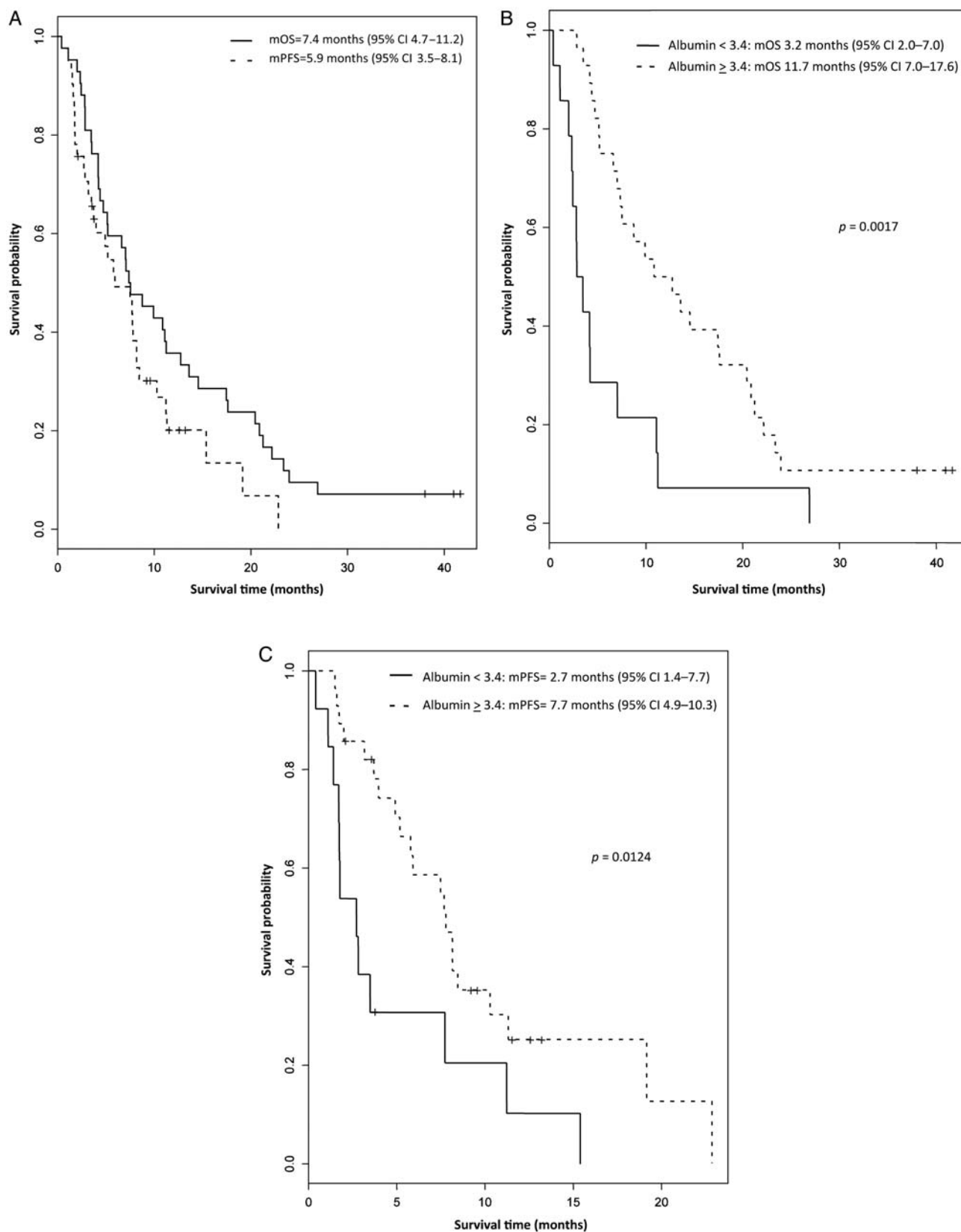[j]42 patients were considered evaluable.

Figure 1. (A) Kaplan–Meier estimation of overall survival (OS) and progression-free survival (PFS). (B) Kaplan–Meier estimation of OS by pretreatment albumin of ≥3.4 versus <3.4 g/dl. (C). Kaplan–Meier estimation of PFS by pretreatment albumin of ≥3.4 versus <3.4 g/dl. mOS, median OS ; mPFS, median PFS.

Table 4. Summary of published phase II and III trials of gemcitabine + antiangiogenic therapy in advanced pancreas cancer

First author	Year	Phase	N	Setting	Investigational therapy[a]	Primary endpoint	P-value	mOS (months)	mPFS (months)	ORR
Kindler [36]	2005	II	52	1st line	Gemcitabine + bevacizumab	ORR	—	8.8	5.4	21%
Spano [62]	2008	II	103	1st line	A: Gemcitabine + axitinib	OS	—	A: 6.9	A: 4.2	A: 7%
					B: Gemcitabine			B: 5.6	B: 3.7	B: 3%
Javle [55]	2009	II	50	1st line	Gemcitabine + capecitabine + bevacizumab	PFS	—	9.8	5.8	22%
Van Cutsem [38]	2009	III	607	1st line	A: Gemcitabine + bevacizumab + erlotinib	OS	0.21	A: 7.1	A: 4.6	A:13.5%
					B: Gemcitabine + erlotinib + placebo			B: 6.0	B: 3.6	B: 8.6%
Kindler [37]	2010	III	602	1st line	A: Gemcitabine + bevacizumab	OS	0.95	A: 5.8	A: 3.8	A: 13%
					B: Gemcitabine + placebo			B: 5.9	B: 2.9	B: 10%
Kindler [55]	2011	III	632	1st line	A: Gemcitabine + axitinib	OS	0.54	A: 8.5	A: 4.4	A: 5%
					B: Gemcitabine + placebo			B: 8.3	B: 4.4	B: 2%
Martin[b]	2011	II	42	1st line	FDR gemcitabine + infusional 5-FU + bevacizumab	6-month PFS	—	7.4	5.9	30%

mOS, median overall survival, mPFS, median progression free survival; ORR, objective response rate (complete + partial response); ORR, objective response rate (complete + partial response); FDR, fixed dose rate.
[a]Gemcitabine, standard 30 min infusion unless otherwise specified.
[b]Current study.

interesting activity is the finding that 59% of patients experienced >25% improvement in CA19-9 levels which has been shown to correlate with a favorable outcome [56–59]. These interesting findings argue for continued investigation of antiangiogenic therapies in PCA.

The choice of a chemotherapeutic backbone may impact the efficacy of antiangiogenic therapy in PCA. In a preclinical study, the antitumor activity of paclitaxel and fluoropyrimidines but not that of gemcitabine caused the release of bone marrow derived circulating endothelial progenitor cells (CEPs) and Tie-2 expressing monocytes (TEMs) as well as the induction of pro-angiogenic growth factors. Anti-angiogenic agents inhibit the CEP and TEM mobilization and proangiogenic signaling and thus enhance significantly the antitumor activity of paclitaxel and fluoropyrimidines but not that of gemcitabine [60]. Additionally, gemcitabine-induced myelosuppression in patients with PCA was found to interfere with the mobilization of proangiogenic cell types targeted by bevacizumab and may further counteract antiangiogenic therapy by substantially reducing the angiogenesis inhibitor TSP-1 [61]. These findings may explain why gemcitabine does not elicit TEM and CEP recruitment and may therefore lack synergy with bevacizumab. This phenomenon is not known to occur with fluoropyrimidines. Clinically, this is reinforced by the fact that in addition to our study, the only other study with a combination of gemcitabine plus bevacizumab in PCA to reach its primary end point included a fluoropyrimidine (Table 4) [54].

Several published phase II and III studies investigated antiangiogenic therapy in combination with gemcitabine in PCA [(36–38, 54, 55, 62), Table 4]. All three phase III studies failed to reach their primary end point of OS. However, in the AViTA trial, there was evidence of significant improvements in PFS with the addition of bevacizumab to gemcitabine and erlotinib [38]. More recently, correlative analyses from this trial revealed improved outcomes in bevacizumab-treated patients

with baseline elevated plasma levels of VEGFA (OS and PFS) and VEGFR2 (OS) [39] supporting a continued interest in VEGF as a valid therapeutic target in a subset of patients in PCA.

It has also been proposed that hypertension can be used as a pharmacodynamic biomarker for the efficacy of VEGF signaling inhibition [63, 64]. An association between bevacizumab-related hypertension and improved efficacy has been observed in multiple studies with bevacizumab [65] or axitinib [62] in PCA and bevacizumab in other malignancies [66–72]. We confirmed that treatment-related hypertension may be a useful biomarker that predicts for favorable outcomes of antiangiogenic therapy in PCA. Further investigation is warranted to understand the utility of this finding in the clinical setting. For example, studies suggest a relationship between dose intensity of bevacizumab and hypertension [73, 74].

Previous pharmacokinetic studies of bevacizumab showed that a low baseline albumin results in a 15%–20% increased clearance of bevacizumab [75, 76] and patients with low albumin levels may be exposed to lower levels of bevacizumab, which potentially may lead to inferior clinical outcomes. We evaluated the role of pretreatment albumin levels as a potential predictive biomarker for the efficacy of bevacizumab in PCA and found a significant association between normal or above-normal levels and improved clinical outcomes. In the absence of a control arm, albumin levels may be prognostic and future controlled studies are needed to confirm a potential predictive role. Future controlled studies are needed to confirm a potential predictive role. If indeed predictive, pharmacokinetic dose adjustments of bevacizumab based on albumin levels may need to be studied further.

The interpretation of our study results is limited by the small number of patients and the lack of control arm. Our *post hoc* subgroup analyses are exploratory in nature and should be interpreted in this limited context.

In conclusion, the combination of bevacizumab with FDR gemcitabine followed by infusional 5-FU is safe and tolerable

with promising activity in PCA. Our results suggest that angiogenesis remains a viable target in PCA, provided that antiangiogenic agents are paired with a rational chemotherapy backbone, such as a fluoropyrimidine-based regimen (including FOLFIRINOX), to maximize the potential for synergism. Future studies should also focus on identifying subsets of patients more likely to benefit from bevacizumab in PCA. Baseline plasma VEGFA/VEGFR2 and albumin levels may be important for appropriate patient selection for bevacizumab therapy. Treatment-related hypertension may predict for improved outcomes of bevacizumab therapy. These strategies deserve to be further investigated in randomized controlled clinical trials.

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disclosures

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Neoadjuvant cetuximab, twice-weekly gemcitabine, and intensity-modulated radiotherapy (IMRT) in patients with pancreatic adenocarcinoma

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Background: Neoadjuvant therapy has been investigated for localized and locally advanced pancreatic ductal adenocarcinoma (PDAC) but no standard of care exists. Combination cetuximab/gemcitabine/radiotherapy demonstrates encouraging preclinical activity in PDAC. We investigated cetuximab with twice-weekly gemcitabine and intensity-modulated radiotherapy (IMRT) as neoadjuvant therapy in patients with localized or locally advanced PDAC.

Experimental design: Treatment consisted of cetuximab load at 400 mg/m^2 followed by cetuximab 250 mg/m^2 weekly and gemcitabine 50 mg/m^2 twice-weekly given concurrently with IMRT to 54 Gy. Following therapy, patients were considered for resection.

Results: Thirty-seven patients were enrolled with 33 assessable for response. Ten patients (30%) manifested partial response and 20 (61%) manifested stable disease by RECIST. Twenty-five patients (76%) underwent resection, including 18/23 previously borderline and 3/6 previously unresectable tumors. Twenty-three (92%) of these had negative surgical margins. Pathology revealed that 24% of resected tumors had grade III/IV tumor kill, including two pathological complete responses (8%). Median survival was 24.3 months in resected patients. Outcome did not vary by epidermal growth factor receptor status.

Conclusions: Neoadjuvant therapy with cetuximab/gemcitabine/IMRT is tolerable and active in PDAC. Margin-negative resection rates are high and some locally advanced tumors can be downstaged to allow for complete resection with encouraging survival. Pathological complete responses can occur. This combination warrants further investigation.

Key words: cetuximab, gemcitabine, intensity-modulated radiotherapy, neoadjuvant therapy, pancreatic cancer

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introduction

Pancreatic ductal adenocarcinoma (PDAC) is highly lethal with 5-year mortality of 95% [1]. Complete resection of localized