An Intergroup Randomized Phase II Study of Bevacizumab or Cetuximab in Combination with Gemcitabine and in Combination with Chemoradiation in Patients with Resected Pancreatic Carcinoma: A Trial of the ECOG-ACRIN Cancer Research Group (E2204)

Jordan D. Berlin^a Yang Feng^b Paul Catalano^b James L. Abbruzzese^c
Philip A. Philip^d Robert R. McWilliams^e Andrew M. Lowy^f Al B. Benson III^g
A. William Blackstock^h

^aVanderbilt-Ingram Cancer Center, Nashville, TN, ^bDana Farber Cancer Institute, Boston, MA, ^cDuke University Medical Center, Raleigh-Durham, NC, ^dKarmanos Cancer Center, Wayne State University, Detroit, MI, ^eMayo Clinic, Rochester, MN, ^fUniversity of California, San Diego, CA, ^gNorthwestern University, Chicago, IL, and ^hWake Forest University, Winston-Salem, NC, USA

Keywords

Resected pancreatic carcinoma · Randomized phase II · Bevacizumab · Cetuximab · Chemoradiation

Abstract

Objectives: Evaluate toxicity of two treatment arms, A (cetuximab) and B (bevacizumab), when combined with gemcitabine, and chemoradiation in patients with completely resected pancreatic carcinoma. Secondary objectives included overall survival (OS) and disease-free survival (DFS). **Methods:** Patients with R0/R1 resection were randomized 1:1 to cetuximab or bevacizumab administered in combination with gemcitabine for two treatment cycles. Next three cycles included concurrent cetuximab/bevacizumab plus chemoradiation, followed by one cycle of cetuximab/beva-

cizumab. Cycles 7–12 included cetuximab/bevacizumab with gemcitabine. Cycles were 2 weeks. Frequency of specific toxicities was summarized for each treatment arm at two times during the study, after chemotherapy but prior to chemoradiation and after all therapy. **Results:** A total of 127 patients were randomized (A, $n = 65$; B, $n = 62$). Prior to chemoradiation, the overall rate for toxicities of interest was 10% for arm A and 2% for arm B. After all therapy, the overall rates for toxicities of interest were 30 and 25% for arms A and B, respectively. Overall median OS and DFS were 17 and 11 months, respectively, which is not a significant improvement over expected survival rates for historical controls. **Conclusions:** Both treatments were tolerable with manageable toxicities, and were safe enough for a phase III trial had this been indicated.

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Introduction

Pancreatic cancer recently rose to the third leading cause of cancer death in the United States and has the potential to replace colorectal cancer as the second leading cause of death in the near future [1]. Although they represent less than 20% of all pancreatic cancer patients, at present, only those with localized, resectable tumors have a chance to be cured through surgery. However, surgery alone results in a 5-year survival rate of approximately 10% [2–6]. Both chemotherapy and combined modality therapy with chemotherapy and chemoradiation have been administered as adjuvant therapy. Survival following adjuvant therapy remains less than 25% at 5 years. Therefore, we need better treatment options in this setting.

In 2004, when this study was designed, the most commonly used adjuvant therapy in the United States was a combination of chemotherapy and chemoradiation as established by Radiation Therapy Oncology Group (RTOG) protocol 97-04 (R9704) [4]. The R9704 regimen incorporated one cycle of gemcitabine weekly for 3 weeks and 1 week of rest. The next treatment cycle included infusional 5-fluorouracil concomitant with 50.4 Gy radiation followed by three more cycles of gemcitabine weekly for 3 weeks and 1 week of rest. This regimen served as the platform upon which modifications were made for this study design.

That same year, two novel targeted agents were tested in the metastatic setting in phase III trials. Southwest Oncology Group (SWOG) protocol S0205 randomly assigned patients with metastatic disease to gemcitabine with or without the addition of cetuximab, while Cancer and Leukemia Group B (CALGB) 80303 investigated gemcitabine versus gemcitabine plus bevacizumab [7, 8]. Both trials were based on the understanding of the molecular biology of pancreatic cancer and built on results of phase II trials. In the case of bevacizumab, the combination with gemcitabine met its study endpoints and provided a very promising median survival exceeding 8 months [9]. For cetuximab, while its primary endpoint in phase II was not met, a promising 1-year survival rate led to its further development [10].

Unfortunately, the subsequent randomized phase III trials for bevacizumab and cetuximab were negative; therefore, this trial was designed to better understand the safety and efficacy of either bevacizumab or cetuximab in the postoperative setting in combination with both chemotherapy and chemoradiation. Neither bevacizumab nor cetuximab had been assessed in the postoperative setting; thus, the primary outcome measure of the current study was toxicity.

Methods

Patient Selection

Patients must have completed an R0 or R1 resection for histologically proven pancreatic adenocarcinoma with no evidence of metastatic disease. Patients were ≥ 18 years old with an ECOG Performance Status of 0–2, had adequate marrow and organ function as follows: absolute neutrophil count $\geq 1,500/\text{mm}^3$, platelet $\geq 100,000/\text{mm}^3$, AST and ALT both $\leq 2.5 \times$ institutional upper limit of normal, and creatinine clearance ≥ 60 ml/min as calculated by Cockcroft-Gault formula or 24-h urine for creatinine clearance. Documentation of the following margins was requested: common bile duct, pancreatic parenchymal, and retroperitoneal or superior mesenteric artery margin. Diagrams were provided in the protocol to define the superior mesenteric artery margin and the superior mesenteric vein margin. If data on all three margins were not available, the margin data that were known were requested; however, lack of data on all three margins was not an eligibility requirement. Patients were ineligible if they had prior chemotherapy or radiation for pancreatic cancer. Patients were not eligible if they had unhealed wounds, prior stroke, or transient ischemic attack. Patients with a history of angina, myocardial infarction or arterial thrombotic events had to be >1 year out from the last event. In addition, patients could not be on therapeutic anticoagulation.

This study was approved by the review boards at all participating institutions, and all subjects provided written informed consent. The study was conducted in accordance with good clinical practice and the Declaration of Helsinki and its amendments. The study was registered through ClinicalTrials.gov (NCT00305877).

Study Schema and Treatment

The study schema is shown in Figure 1. This was an open-label, unblinded, 1:1 randomization to either cetuximab or bevacizumab. The doses of cetuximab and bevacizumab were chosen based on the prior phase III studies of each agent in combination with gemcitabine [7, 8]. Patients in arm A received cetuximab 400 mg/m² on day 1 of cycle 1 of chemotherapy; all subsequent doses were 250 mg/m² weekly with infusion rate ≤ 5 mL/min. Since there were no safety data for a 10 mg/kg dose of bevacizumab every other week during radiation to the pancreas, patients were treated at a dose of 5 mg/kg every other week until they completed radiation. Then the dose was escalated to 10 mg/kg every other week for the completion of chemotherapy. The dose for capecitabine during radiation was based on a prior clinical trial [11].

In both arms, gemcitabine 1,000 mg/m² was initiated weekly for 3 weeks followed by 1 week of rest. Presuming no significant adverse events, capecitabine 825 mg/m² twice daily was initiated after the week of rest, to be taken on days of radiation. Radiation therapy (RT) was administered 5 days per week in 25 fractions to a total dose of 4,500 cGy followed by a boost of 540 cGy administered over 3 days. After recovery from radiation, patients on both arms had three additional cycles of 1,000 mg/m²/week gemcitabine for 3 weeks followed by 1 week of rest. Dose modifications of radiation, chemotherapy, or experimental drugs were allowed.

Three-dimensional conformal radiation planning was performed on this study. Intensity-modulated radiotherapy was not allowed. Tumor volumes and treatment planning was fully described in the protocol and after enrollment, films were submitted to the Quality Assurance Review Center for central review to as-

Fig. 1. Study schema.

Fig. 2. CONSORT diagram.

sure adherence to the protocol. Baseline CT scans were allowed if they were collected within 10 weeks prior to initiating therapy; thus, some patients did not have postoperative evaluations prior to starting adjuvant therapy. After completion of all therapies, patients were followed for progression or death with scans every 6 months for 3 years, then scans every year for 2 years.

Statistical Design

The primary endpoint of this study was toxicity. Due to separate components of gemcitabine and combined modality chemoradiation, toxicity was evaluated at several time points to assess safety of cetuximab and/or bevacizumab with each component of the regimen. Therefore, formal evaluation of toxicities was report-

Table 1. Patient demographics and clinical characteristics

	Total	Arm A	Arm B	<i>p</i> value
Patients, <i>n</i>	130	67	63	0.82 (K)
Age, years				
Median	59	59	59	
Minimum	29.2	29.2	41.6	
Maximum	92.9	92.9	79.4	
Sex, <i>n</i> %				
Male	65 (50.0)	32 (47.8)	33 (52.4)	0.73 (P)
Female	65 (50.0)	35 (52.2)	30 (47.6)	
Race and ethnicity, <i>n</i> (%)				
Hispanic	3 (2.3)	0	3 (4.8)	0.37 (E)
Non-Hispanic White	112 (86.2)	58 (86.6)	54 (85.7)	
Non-Hispanic Black	9 (6.9)	5 (7.5)	4 (6.4)	
Other	6 (4.6)	4 (6.0)	2 (3.2)	
Histological grade, <i>n</i> (%)				
Missing/unknown	1 (0.8)	1 (1.5)	0	0.16 (E)
Well differentiated (grade I)	13 (10.0)	3 (4.5)	10 (15.9)	
Moderately differentiated (grade II)	75 (57.7)	41 (61.2)	34 (54.0)	
Poorly differentiated (grade III)	39 (30.0)	21 (31.3)	18 (28.6)	
Undifferentiated (grade IV)	2 (1.5)	1 (1.5)	1 (1.6)	
Pancreas primary site, <i>n</i> (%)				
Head of pancreas	105 (80.8)	54 (80.6)	51 (81.0)	0.59 (E)
Body of pancreas	8 (6.2)	6 (9.0)	2 (3.2)	
Tail of pancreas	8 (6.2)	3 (4.5)	5 (7.9)	
Uncinate process	2 (1.5)	1 (1.5)	1 (1.6)	
Diffuse	3 (2.3)	2 (3.0)	1 (1.6)	
Pancreas, NOS	4 (3.1)	1 (1.5)	3 (4.8)	
ECOG Performance Status, <i>n</i> (%)				
0	59 (45.4)	28 (41.8)	31 (49.2)	0.20 (E)
1	69 (53.1)	39 (58.2)	30 (47.6)	
2	2 (1.5)	0	2 (3.2)	
Resected surgical margins, <i>n</i> (%)				
R0	92 (70.8)	44 (65.7)	48 (76.2)	0.25 (F)
R1	38 (29.2)	23 (34.3)	15 (23.8)	

K, Kruskal-Wallis test; P, Pearson's χ^2 test; F, Fisher's exact test; E, exact test for RxC tables.

ed after chemotherapy prior to Chemo/RT (time point 1), and after completion of all therapy (time point 2). Additionally, institutions were required to report and summarize toxicity experience for all three major treatment periods: after chemotherapy prior to Chemo/RT, after Chemo/RT, and at the conclusion of all therapy.

Toxicities were evaluated separately in each treatment arm as the study was not powered to provide meaningful comparisons of adverse events between treatment arms. For each toxicity evaluation (time points 1 and 2), toxicity occurrence was quantified. From the most relevant literature on prior studies in adjuvant and advanced disease using the proposed agents and regimens, an overall true adverse event rate of 20% for the toxicities was for time point 1 above. Equal randomization of 120 eligible patients (60 per arm) provided 85% power to detect a true unacceptable adverse event rate of 35% using a one-sided 9% level exact binomial test for time point 1 in each treatment arm. Formal toxicity evaluation also occurred at time point 2. It was expected that an overall adverse event rate of 25% was considered expected and acceptable for time point

2. With 60 eligible patients per arm, there was greater than 85% power to detect an unacceptable adverse event rate of 45% using a one-sided 9% level exact binomial test for time point 2. Toxicity rate was based on designated side effects of interest as listed below.

A two-stage design was employed in this trial, within each treatment arm, to evaluate the adverse events of $\geq$ grade 4 toxicities (dyspnea, neutropenic fever, allergic reaction, rash, wound dehiscence, wound infection, hypertension), $\geq$ grade 3 toxicities (arterial thromboembolic phenomena (TIA, CVA, MI, angina), bleeding, phlebitis/DVT/PE, hemorrhage, ileus, bowel perforation, diarrhea, mucositis) and other toxicities (ECOG Performance Status decline by 2+ for >24 h and weight loss $>10\%$ ($\geq$ grade 2) at time point 1 for potential early termination of one or both arms of the trial in the case of excessive toxicity. After 25 patients per arm had completed therapy for time point 1, the study was put on hold to evaluate toxicities. It was planned that if, using the above events, 18 or more patients were event-free in the first 25 patients on either arm, the respective arm(s) would be suspended and detailed toxic-

Table 2. Overall toxicity by treatment arm: most frequently ($\geq 20\%$) occurring adverse events after completion of all therapy

Adverse event	Arm A (<i>n</i> = 67)				Arm B (<i>n</i> = 63)			
	all grades		grade $\geq 3^a$		all grades		grade $\geq 3^b$	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Rash/desquamation	56	84	12	18	10	16	0	0
Nausea	43	64	3	4	39	62	2	3
Fatigue	50	75	11	16	49	78	6	10
Thrombocytopenia	36	54	4	6	36	57	9	14
Diarrhea without prior colostomy	35	52	5	7	29	46	1	2
Hypoalbuminemia	33	49	3	4	18	29	2	3
Anorexia	31	46	3	4	20	32	4	6
Elevated AST	34	51	6	9	24	38	0	0
Elevated hemoglobin	28	42	2	3	29	46	4	6
Vomiting	29	43	3	4	13	21	1	2
Elevated alkaline phosphatase	27	40	1	1	15	24	1	2
Leukocytopenia	50	75	25	37	40	63	24	38
Hand-foot reaction	28	42	3	4	9	14	0	0
Abdominal pain	23	34	0	0	23	37	4	6
Elevated ALT	28	42	6	9	20	32	0	0
Oral mucositis	21	31	0	0	10	16	0	0
Pruritus/itching	22	33	2	3	3	5	0	0
Hypocalcemia	19	28	1	1	10	16	1	2
Hypomagnesemia	18	27	0	0	0	0	0	0
Weight loss	17	25	0	0	15	24	2	3
Fever without neutropenia	16	24	0	0	10	16	0	0
Neutropenia	44	66	29	43	50	79	35	56
Alopecia	15	22	0	0	12	19	0	0
Constipation	14	21	0	0	11	17	0	0
Dry skin	14	21	1	1	0	0	0	0
Hyperglycemia	14	21	1	1	7	11	2	3
Hypertension	1	1	0	0	16	25	3	5

^a Other grade 3/4 events reported were: lymphocytopenia (*n* = 10), infection (*n* = 5), dehydration (*n* = 4), rash acneiform (*n* = 3), thrombosis/embolism (*n* = 3), nail changes (*n* = 2), elevated bilirubin (*n* = 2), and hypokalemia, hyponatremia, infection, nonmalignant ascites, other hepatic toxicity, febrile neutropenia, liver infection with unknown ANC, other infection, hyperuricemia, and allergic reaction occurring in 1 patient each. ^b Other grade 3/4 events reported were: lymphocytopenia (*n* = 7), thrombosis/embolism (*n* = 4), hyperglycemia (*n* = 2), dehydration (*n* = 2), hypokalemia (*n* = 2), and hypocalcemia, rigors/chills, neuropathy, elevated creatinine, dizziness, hypoglycemia, confusion, gastritis, supraventricular tachycardia, enteritis, gastric ulcer, febrile neutropenia, syncope, proteinuria infection, and C-P arrest occurring in 1 patient each. One patient experienced a grade 5 colon perforation that was determined to be definitely related to bevacizumab and possibly related to radiation.

ity data reviewed for possible closure of the arm. If the true toxicity rate for events was 35% or higher, there was at least a 0.69 probability of stopping the arm after the first 25 patients. If the study criteria were met allowing opening of the second stage, accrual would begin after the first 25 patients had finished chemo/RT and all toxicity data had been reviewed with the sponsor.

Overall survival (OS) and disease-free survival (DFS) were secondary endpoints. OS was defined as the time from randomization to death from any cause, or censored at last known date of survival. DFS was defined as the time from randomization to the first treatment failure (recurrence or death before recurrence). No formal comparisons in survival or DFS between arms were made.

Results

From February 2006 to January 2008, 137 patients were enrolled (Fig. 2). Patient characteristics are shown in Table 1 with no significant differences between the two arms. Of the 137 patients, 10 never started the assigned therapy: 5 were ineligible, 2 refused assigned treatment, 1 had an accident requiring surgery prior to starting therapy, 1 had disease progression prior to starting therapy, and 1 received hospital stock instead of study supply

Fig. 3. Kaplan-Meier curves. Estimates of overall survival (a) and disease-free survival (b) for treatment arms A and B.

drug. Of the ineligible patients, 3 patients had elevated bilirubin, ampullary primary in 1 patient, and 1 patient started RT prior to initiating therapy on trial. The efficacy analysis was based on the 127 eligible patients who started therapy, and the safety analysis includes all patients who started therapy.

Safety Analysis

Toxicity was the primary endpoint of this trial, which was assessed at 2 time points. At postchemotherapy prior to Chemo/RT, the overall rate for specific protocol-defined adverse event was 10% (95% two-stage confidence interval [CI] for 7 cases out of 67: 4, 20%) for arm A and 2% (95% two-stage CI for 1 case out of 63: 0.1–9%) for arm B. At the conclusion of all therapy, the overall rate for specific protocol-defined adverse event was 30% (95%

two-stage CI for 20 cases out of 67: 19–42%) for arm A and 25% (95% two stage CI for 16 cases out of 63: 15–38%) for arm B. Both arms seem safe, and side effects were manageable in this trial. Both drugs appeared safe enough to go on to phase III trial had this been indicated. Table 2 lists common (occurring $\geq 20\%$) toxicities by grade for both arms.

Efficacy Analysis

The median OS was 17 months (95% CI 14–21) for the two arms (Fig. 3a). Two-year OS for all patients was 37% (95% CI 29–45%). Two-year OS for the two treatment arms A (cetuximab) and B (bevacizumab) were 38% (95% CI 26–50%) and 37% (95% CI 24–48%), respectively. The median DFS was 11 months (Fig. 3b; 95% CI 9–13). Two-year DFS for all patients was 20% (95% CI 13–27%). Two-year DFS for the two treatment arms A and B were 17% (95% CI 8–26%) and 23% (95% CI 12–34%), respectively. No formal comparisons in OS or DFS between arms were made, as this was not part of the trial design. Although this was not a randomized phase II comparator trial, the arms appeared similar in efficacy.

Treatment Delivery

In arm A, 69.2% of patients received all protocol therapy, while in arm B 54.8% received all therapy. Radiation dosing was not impacted as the median and mean for doses and number of fractions received was the total planned. Reasons patients discontinued treatment in arm A were disease progression ($n = 6$, 9.2%), toxicity ($n = 9$, 13.8%), and other ($n = 5$, 7.7%). The reasons patients discontinued treatment in arm B were disease progression ($n = 9$, 14.5%), toxicity ($n = 14$, 22.6%), death ($n = 1$, 1.6%) and other ($n = 4$, 6.5%). Three patients died while on study, 2 due to disease progression, but 1 patient experienced a grade 5 colonic perforation that was definitely attributed to bevacizumab and possibly related to radiation.

Discussion

The median survivals for both arms were lower than for any of the chemotherapy alone randomized phase III trials published since this trial started, but very comparable to the chemoradiation results from ESPAC-1 and RTOG 9704 [2, 4]. It is possible that the current smaller study differed from chemotherapy alone studies due to random chance, differences in patients, or a myriad of other reasons; however, it is also possible that these

shorter median survivals were real. While cross-trial comparison is not fully reliable, the median survivals on this trial raised significant concerns. Considering the comparability of the arms of this trial with the results for R9704 upon which this study was based, it is possible that as suggested by ESPAC-1, the early incorporation of radiation into the adjuvant therapy of pancreatic cancer confers a poorer survival outcome [6, 10]. Because this is largely a systemic disease, focusing on the local therapy too soon may compromise the effective use of systemic therapy. Alternatively, both of the novel agents may have had a negative impact on the postoperative outcomes. In colon cancer, cetuximab had a detrimental impact on patients with Ras-mutated stage III disease receiving FOLFOX chemotherapy [12]. While we did not assess for Ras mutations, approximately 90% of pancreatic adenocarcinomas have a Ras mutation [13]. Similarly, in the AVANT trial in colon cancer, bevacizumab did not add to the efficacy of adjuvant FOLFOX, and there was a suggestion that a minimal detriment may have occurred [14]. Finally, it is possible that the treatment arms were overall too toxic causing too many dose reductions in the chemotherapy. As shown, 30.8% in arm A and 45.2% of patients in arm B did not receive full planned therapy. In an analysis of the ESPAC-3 trial, it was demonstrated that receiving all doses of chemotherapy was favorable for prognosis, while delaying chemotherapy initiation had no impact on prognosis [15]. Thus, the possible detriment in median survivals seen with these regimens may have simply been their impact on patient completion of therapy. If chemoradiation was the cause of diminished dose delivery, then these results strongly support the study design of RTOG 0848 (NCT01013649), an important ongoing randomized trial assessing the role of chemoradiation at the end of adjuvant chemotherapy.

Of note, our primary endpoint was one of tolerance of these drugs after surgery, and that endpoint was met as neither drug caused significant increases in the toxicities of interest selected by the investigators. We selected the side effects of interest in the perioperative setting that would have made early administration of either bevacizumab or cetuximab unsafe. This study design was successful in that it allowed us to answer the questions we asked. As a potential weakness, there may have been side effects of these agents specific to the perioperative setting that we did not set up a priori to capture, and something may have been missed that made these agents unsafe. However, the overall safety profile was reasonable making this an unlikely scenario.

This trial demonstrated the feasibility of doing smaller randomized phase II trials of novel agents in the adjuvant setting for pancreatic cancer. This study met its target accrual rate and answered the primary questions posed while providing enough efficacy data that had bevacizumab or cetuximab been effective in metastatic disease, these results alone would have likely prevented the advancement of either arm to a larger trial in the adjuvant setting.

Conclusions

While the administration of either cetuximab or bevacizumab in combination with “sandwich” chemoradiation is feasible and safe, the efficacy of the two regimens suggests that no further study is warranted. However, the use of novel agents in smaller, feasibility studies in the adjuvant therapy of pancreatic cancer is reasonable and should be considered for drugs demonstrating sufficient clinical activity. Chemoradiotherapy still needs to be assessed for efficacy after the completion of chemotherapy.

Acknowledgements

This study was coordinated by the ECOG-ACRIN Cancer Research Group (Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported in part by Public Health Service Grants CA180820, CA180794, CA180847, CA180790, CA03927, CA180857, CA31946, CA32102, CA38926 CA180888, CA180819, CA76429, CA25224, and from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Disclosure Statement

J.D.B. has served as a consultant for Celgene, Genentech, Aduro, Janssen, Cornerstone, Symphogen, and Bayer and has institutional research funding from Genentech, Abbvie, Taiho, Bayer, 5 Prime, Phoenix, Incyte, and Vertex. A.M.L. is a consultant for Halozyme Therapeutics and has received research support from Syros and Tanabe-Mitsubishi. P.C. is a consultant on a data safety monitoring and board member with Lilly. All other authors have no conflicts to disclose.

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