Medicine®

OBSERVATIONAL STUDY

OPEN

Combination of Two Targeted Medications (Bevacizumab Plus Cetuximab) Improve the Therapeutic Response of Pancreatic Carcinoma

Cheng-Jeng Tai, MD, PhD, Ming-Te Huang, MD, Chih-Hsiung Wu, MD, PhD, Chien-Kai Wang, PhD, Chen-Jei Tai, MD, PhD, Chun-Chao Chang, MD, Cheng-I. Hsieh, MD, Yu-Jia Chang, PhD, Chang-Jer Wu, PhD, Li-Jen Kuo, MD, Po-Lei Wei, MD, PhD, Ray-Jade Chen, MD, and Hung-Yi Chiou, PhD

Abstract: The objective of this study is to evaluate the efficacy and safety profiles of the targeted medications, bevacizumab and cetuximab, in combination with cytostatic drugs in patients with locally advanced or metastatic pancreatic cancer.

In this retrospective phase 2 study, a total of 59 patients with pancreatic cancer were recruited and received conventional (gemcitabine, cisplatin, and fluorouracil) or targeted regimen (conventional plus bevacizumab and cetuximab for the first cycle) in 2-week intervals for four cycles. The primary end-point for this study was the overall response rate. Secondary end-points were progression-free survival and the safety profiles of the combined therapy.

The median time-to-progression and overall survival were 3 and 7 months, respectively, in the conventional treatment group as well as 11 and 13 months, respectively, in the targeted medications treatment group. The most common adverse events in both treatment groups were nausea and vomiting. Moderate (Grade 2) nausea and vomiting were more common in the conventional group than the targeted group but severe (Grade 3) nausea and vomiting were more common in the targeted group.

Bevacizumab and cetuximab in combination with gemcitabine, cisplatin, and fluorouracil may help lengthen overall survival up to six months for patients with pancreatic cancer.

(*Medicine* 95(15):e3259)

Abbreviations: ANC = absolute neutrophil count, CT = computerized tomography, CTCAE = common terminology criteria for adverse events, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, FOLFIRINOX = 5-fluorouracil, leucovorin, oxaliplatin, irinotexan, NAB-P = gemcitabine with albumin-bound paclitaxel, RECIST = Response Evaluation Criteria in Solid Tumors, SD = standard deviations, ULN = upper limit of normal, VEGF = vascular endothelial growth factor.

INTRODUCTION

Unresectable, locally, advanced pancreatic cancer has a poor prognosis and is the 13th most common cancer and the 8th leading cause of cancer worldwide.[1] The 5-year survival rate for patients with pancreatic cancers ranges from 0.4% to 4%.[1,2] Median survival time for patients with advanced metastatic disease is only ~4 to 12 months.[3–5] Although surgical resection can improve survival and provides the only chance for cure, only ~10% of patients with pancreatic cancer are eligible for resection.[4,6,7]

Presently, there is no consensus on the treatment of locally advanced pancreatic cancer. Typically patients are treated with 5-fluorouracil-based chemoradiation or gemicitabine-based chemotherapy alone.[8] Since the 1990s, gemicitabine has been the primary therapeutic agent for pancreatic cancer.[9] Current treatment regimens include 5-fluorouracil, leucovorin, oxaliplatin, irinotexan (FOLFIRINOX), and gemcitabine with albumin-bound paclitaxel (NAB-P). These therapies offer survival benefit of only a few months and are associated with significant toxicities.[10,11]

New approaches to treating pancreatic cancer are emerging because of the increasing understanding of the underlying molecular biology of the disease.[12] Over-expression of epidermal growth factor (EGFR) is common in pancreatic cancer and may result in the aberrant activity of downstream pathways leading to tumor progression.[10] Over-expression of EGFR is associated with increased tumor aggressiveness and poor survival.[13–15] EGFR also promotes radioresistance by stimulating DNA repair by

Editor: Simona Gurzu.
Received: October 23, 2015; revised: January 30, 2016; accepted: March 11, 2016.
From the Division of Hematology and Oncology, Department of Internal Medicine, Taipei Medical University Hospital (C-JT, C-KW, C-CC, C-IH); Department of Internal Medicine (C-JT, C-KW, C-IH); Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University (M-TH, L-JK, P-LW, RJC); Division of General Surgery, Department of Surgery, Shuang Ho Hospital (M-TH, C-HW); Center of Excellence for Cancer Research, Taipei Medical University (C-HW); Department of Surgery, Taipei Medical University-Shuang Ho Hospital (C-HW); Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University (C-KW, C-JT); Department of Chinese Medicine (C-KW, C-JT); Traditional Herbal Medicine Research Center (C-KW, C-JT); Division of Gastroenterology, Department of Internal Medicine (C-CC); Cancer Research Center, Taipei Medical University Hospital (Y-JC); Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University (Y-JC, L-JK, P-LW); Division of General Surgery, Department of Surgery, Taipei Medical University Hospital, Taipei (Y-JC, L-JK, P-LW, R-JC); Department of Food Science (C-JW); Center of Excellence for the Oceans, National Taiwan Ocean University, Keelung (C-JW); Program for Cancer Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University (P-LW); and School of Public Health, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan (H-YC).
Correspondence: Cheng-Jeng Tai, Division of Hematology and Oncology, Department of Internal Medicine, Taipei Medical University Hospital and Division of Hematology and Oncology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan (e-mail: cjtai@tmu.edu.tw).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003259

ionizing radiation.[16,17] Cetuximab (Erbitux®; Bristol-Meyers Squibb, Lawrenceville, NJ) is an EGFR-specific chimeric IgG1 monoclonal antibody that inhibits EGFR-mediated signals transduction and radiation-induced repair.[18] In addition, bevacizumab (Avastin®; Genentech, South San Francisco, CA), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), inhibits tumor growth by inhibiting angiogenesis.[19] Bevacizumab has demonstrated modest anti-pancreatic tumor activity but has not resulted in improvement in survival either alone or in combination with gemcitabine.[19,20] Addition of cetuximab to gemcitabine did result in modest but statistically significant improvement in overall survival compared with gemcitabine therapy alone.[20]

Blocking both the EGFR and VEGF pathways with the combination of cetuximab and bevacizumab in mice carrying human pancreatic xenografts showed a greater inhibition of tumor growth and metastasis than either agent alone.[21] However, a phase 2 study in patients with locally advanced or metastatic pancreatic cancer did not find any survival benefit with the combination of cetuximab and bevacizumab, either with or without gemcitabine.[11] Here we report the findings of a phase 2 study that further evaluated the therapeutic effect of the combination of cetuximab and bevacizumab in pancreatic cancer when added to conventional chemotherapy.

METHODS

This retrospective, phase 2, two-armed study was performed between 2003 and 2009 in patients with unresectable (stage IV) pancreatic cancer. Patients were recruited from the Taipei Medical University Hospital. The study was approved by the hospital's institutional review board and was performed in accordance with the Declaration of Helsinki. All of the patients gave their written informed consent.

Study Patients

Patients were required to be $\geq$18 years of age, have an Eastern Cooperative Oncology Group (ECOG) status $\leq$4, and have histological or cytologically confirmed pancreatic adenocarcinoma, which was not amenable to curative treatment with surgery or had been documented or suspected of metastases to extrapancreatic sites. Included patients had either measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) or nonmeasurable disease with an elevated baseline CA19–9 level ($\geq$2 times the upper limit of normal [ULN]). Patients were required to have adequate renal function as defined by serum creatinine $\leq 2.0 \times$ ULN and urine dipstick for proteinuria $\leq$1+ obtained within 2 weeks before the first dose of study medication. Patients had to have hematologic function as defined by an absolute neutrophil count (ANC) $\geq$1500/mm^3 and a platelet count $\geq$100,000/mm^3 obtained within 2 weeks before the first dose of study medication. Included patients had to have adequate coagulation function and have no active bleeding or pathological condition that carried a high risk of bleeding. Patients were excluded if they had endocrine tumors or lymphoma of the pancreas, or had a concurrent malignancy other than nonmelanomatous skin cancer or cervical cancer. Patients were excluded if they had known brain metastasis.

Study Design

The study included two treatment groups both of which received chemotherapy in 2-week intervals for 12 cycles: in one group patients received conventional therapy (leucovorin, gemcitabine, cisplatin, and fluorouracil), and in the targeted group, patients were given conventional therapy plus bevacizumab and cetuximab in each cycle. The decision of which treatment was administered was dependent upon the patient's consent following discussion between the patient and the physician regarding the two treatments. Patients in the conventional treatment arm were given the regimen as 1000 mg/m^2 gemcitabine and 50 mg/m^2 cisplatin for the first day and on days 8 and 15. The treatment interval for each cycle was 21 days. Patients in the targeted group received on Day 1 gemcitabine and cisplatin similar to the conventional group and also received 5 mg/kg bevacizumab (at 8 mg/kg in the first cycle) with 200 mg/m^2 cetuximab (at 350 mg/m^2 in the first cycle) but did not receive gemcitabine on the Day 8 or 15. The treatment interval was 14 days which was based on the activity of each targeted medication to allow for the proper cycles of treatments and 1 day of the de Gramond regimen of high dose fluorouracil plus leucovorin. If a patient experienced severe or $\geq$grade III adverse effect, the chemotherapy could have been postponed for 1 week. If the adverse effect happened twice consecutively, then the dose was reduced by 20%.

If after treatment, a patient became eligible for surgery, the chemotherapy was stopped and the surgery was performed. One month following surgery, the patient received adjuvant chemotherapy.

Overall survival and progression-free survival were monitored over the 6-year study period and safety was evaluated throughout the study. Disease progression was monitored by computerized tomography (CT) scan every 3 months and disease response was determined according to RECIST criteria.[22] Toxicities were evaluated using the common terminology criteria for adverse events (CTCAE) v4.

Statistical Analysis

The primary endpoint was the overall survival. Secondary endpoints were progression-free survival and the safety profiles of the combined therapy. Continuous variables (i.e., age, time to progression, and survival time) were presented as means and standard deviation (SD), with independent *t* tests used for group comparisons. Categorical variables such as gender, surgery, and adverse events were presented as counts and percentages and chi-square tests or Fisher's exact tests were used for group comparisons. Kaplan–Meier curves with log-rank tests were performed to compare the differences between conventional and targeted groups in progression-free survival and overall survival. Statistical analyses were performed using the IBM SPSS statistical software version 22 for Windows (IBM Corp., Armond, NY), and the two-tailed P value < 0.05 was considered significant.

RESULTS

Patient Demographic

A total of 59 patients were included in this study. Twenty-eight subjects received conventional therapy and 31 subjects were given targeted therapy (conventional plus bevacizumab and cetuximab). Demographics were similar between treatment groups and the mean age was ~56 years. There was a greater percentage of males in the conventional compared with the targeted group (60.7% vs. 41.9%, respectively); however, this did not reach statistical significance ($P = 0.15$).

Time to disease progression was ~10.7 months longer with targeted treatment compared with conventional therapy

TABLE 1. Patient Demographics

	Conventional (n = 28)	Targeted (n = 31)	*P* Value
Age (years)	56.86 ± 13.26	54.84 ± 8.32	0.493
Gender			0.15
Man	17 (60.7%)	13 (41.9%)	
Woman	11 (39.3%)	18 (58.1%)	
Time to progression (months)	3.11 ± 1.69	10.71 ± 13.69	0.004*
Survival time (months)	6.79 ± 2.99	13.23 ± 15.5	0.03*
Surgery	11 (39.3%)	12 (38.7%)	0.964

*$P < 0.05$, significant difference between two groups.

($P = 0.004$) and survival time was ~13.2 months longer with targeted treatment ($P = 0.03$) (Table 1). Overall, a similar percentage of patients received surgery ($P = 0.964$). Before treatment, all 11 patients in the conventional group had surgery. However, all 11 patients had cancer recurrence. In the targeted therapy group, 5 of the 12 patients had surgery before treatment. Following targeted therapy, the tumor of the other seven patients was reduced, which made it possible to remove the tumors by surgery.

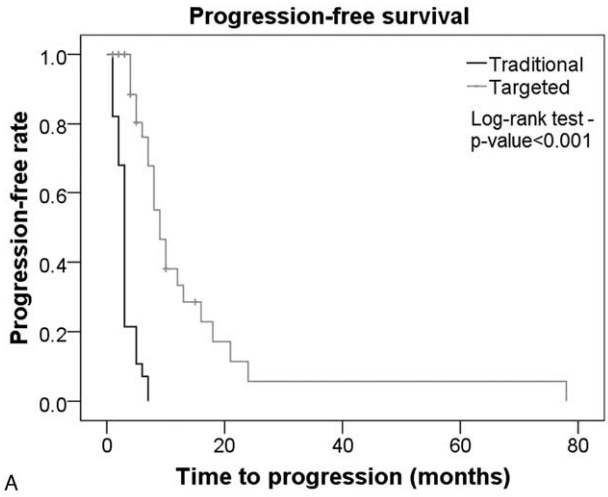
Adverse Events

The most common adverse events in both treatment groups were nausea and vomiting (Table 2). Moderate (Grade 2) nausea and vomiting were more common in the conventional group than the targeted group (92.9% vs. 9.7%, respectively) and severe (Grade 3) nausea and vomiting was more common in the targeted group (7.1% vs. 74.2%) ($P < 0.001$). There was no difference in the frequency of diarrhea, neutropenia, anemia, thrombocytopenia, gastrointestinal tract bleeding, renal, cardiac, and neurolotic

TABLE 2. Summary of Adverse Events

	Conventional (n = 28)	Targeted (n = 31)	*P* Value
Nausea and vomiting			<0.001*
Grade 2: Moderate	26 (92.9%)	3 (9.7%)	
Grade 3: Severe	2 (7.1%)	23 (74.2%)	
Grade 4: Life-threatening	0 (0%)	5 (16.1%)	
Diarrhea			0.539
Grade 1: Mild	7 (25%)	10 (32.3%)	
Neutropenia			0.702
Grade 1: Mild	10 (35.7%)	12 (38.7%)	
Grade 2: Moderate	10 (35.7%)	13 (41.9%)	
Anemia			0.431
Grade 1: Mild	14 (50%)	14 (45.2%)	
Grade 2: Moderate	2 (7.1%)	4 (12.9%)	
Grade 3: Severe	2 (7.1%)	6 (19.4%)	
Thrombocytopenia			0.570
Grade 1: Mild	13 (46.4%)	12 (38.7%)	
Grade 2: Moderate	3 (10.7%)	4 (12.9%)	
Grade 3: Severe	2 (7.1%)	6 (19.4%)	
GI tract bleeding			0.220
Grade 1: Mild	10 (35.7%)	14 (45.2%)	
Grade 2: Moderate	1 (3.6%)	5 (16.1%)	
Grade 3: Severe	1 (3.6%)	1 (3.2%)	
Renal			0.239
Grade 1: Mild	28 (100%)	28 (90.3%)	
Grade 2: Moderate	0 (0%)	3 (9.7%)	
Cardiac			0.101
Grade 1: Mild	2 (7.1%)	0 (0%)	
Grade 2: Moderate	1 (3.6%)	0 (0%)	
Neurolotic toxicities			0.180
Grade 1: Mild	18 (64.3%)	18 (58.1%)	
Grade 2: Moderate	4 (14.3%)	10 (32.3%)	

*$P < 0.05$, significant difference between two groups.GI = gastrointestinal.



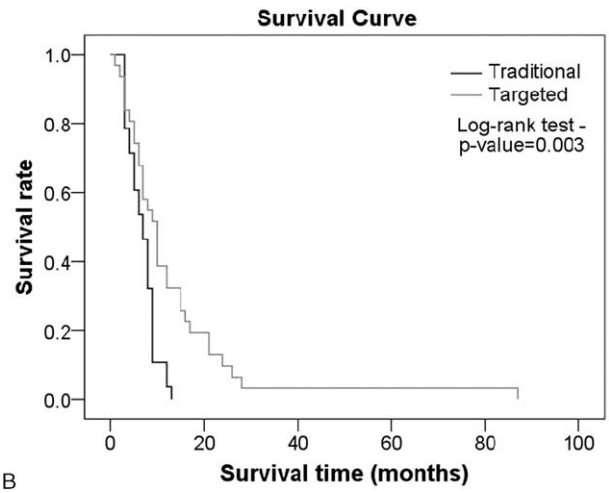
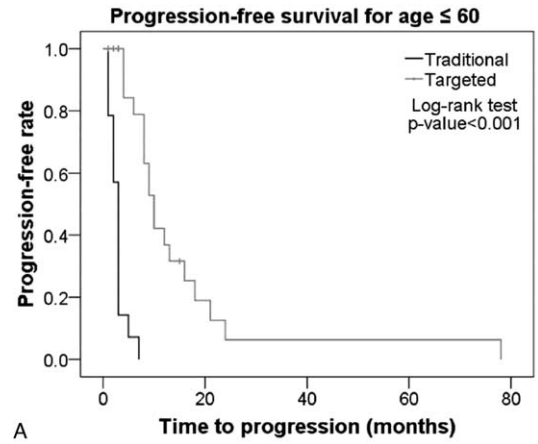


FIGURE 1. (A) Progression free survival rates between different treatments. (B) Overall survival rates between different treatments.



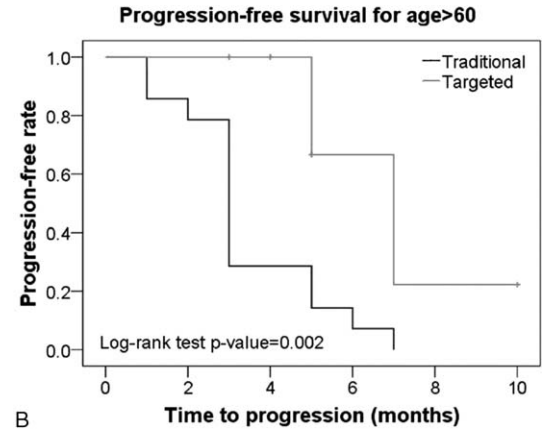


FIGURE 2. (A) Progression free survival rates between different treatments for patients ≤60 years of age. (B) Progression free survival rates between different treatments for subjects >60 years of age.

toxicities between treatment groups ($P > 0.05$). No patients experienced an infection following either treatment regimen.

Progression Free Survival and Overall Survival

Progression-free and overall survival was significantly longer in subjects with targeted treatment compared with those with conventional treatment (Figure 1A and B). Kaplan–Meier curve analysis indicated that the median time to disease progression was approximately 3 months in subjects treated with conventional treatment and ∼9 months in those who received targeted treatment ($P < 0.001$) (Figure 1A). Longer progression-free survival was observed in the targeted treatment group compared with the conventional group for subjects aged ≤60 years (10 months vs. 3 months, respectively; $P < 0.001$) or >60 years of age (7 months vs. 3 months; $P = 0.002$) (Figure 2A and B). Kaplan–Meier analysis found that the median overall survival time was ∼7 months with conventional treatment and ∼10 months with targeted treatment for the entire population ($P = 0.003$) (Figure 1B). Similar to progression-free survival, targeted therapy was associated with longer overall survival than conventional therapy in patients ≤60 years of age (12 months vs. 5 months, respectively; $P = 0.002$) (Figure 3A). However, there was no difference in overall survival between treatment groups in patients >60 years of age ($P > 0.05$) (Figure 3B).

DISCUSSION

This phase 2 study evaluated the efficacy of the combination of cetuximab and bevacizumab in patients with advanced pancreatic cancer. We found that progression-free survival and overall survival were longer in patients treated with the conventional therapy plus cetuximab and bevacizumab compared with patients who received only conventional therapy. The addition of cetuximab and bevacizumab increased progression-free survival by ∼6 months and extended overall survival by ∼3 months. The benefit for progression-free survival was independent of age, whereas the benefit for overall survival was primarily in patients aged ≤60 years. The group of patients who received conventional treatment plus cetuximab and bevacizumab had a higher frequency of severe (Grade 3) nausea and vomiting than the conventional treatment group (74.2% vs. 7.1%, respectively). All other toxicities were similar between treatment groups. These findings suggest that the addition of cetuximab and bevacizumab to conventional therapy may give important benefit in treating patients with advanced pancreatic cancer.

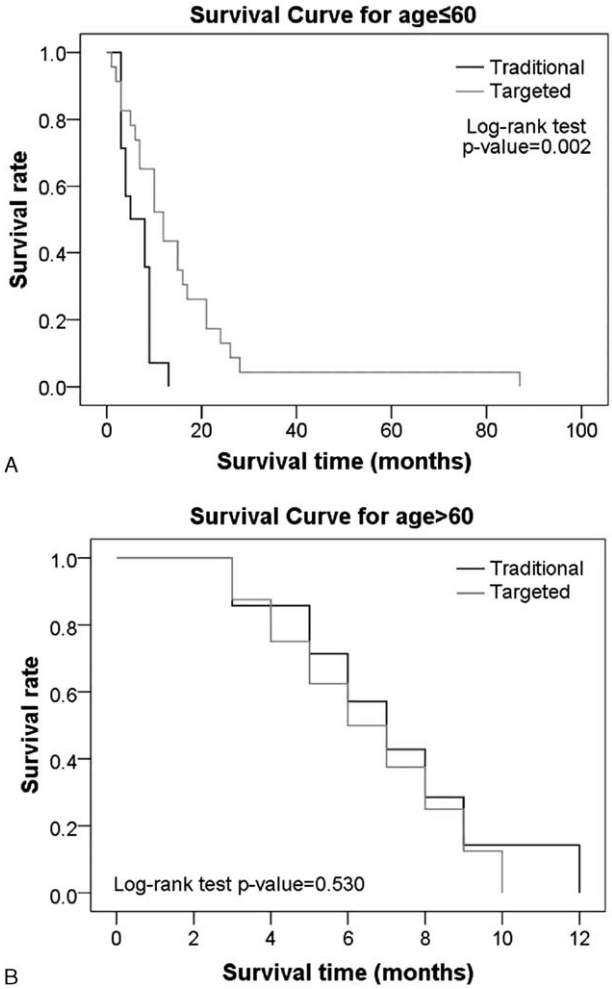


FIGURE 3. (A) Overall survival rates between different treatments for patients ≤60 years of age. (B) Overall survival rates between different treatments for subjects >60 years of age.

A number of randomized controlled trials have investigated the efficacy of the combination of new-targeted agents with chemotherapy in treating patients with pancreatic cancer.[20] However, most have shown disappointing results.[20] One meta-analysis, which included six studies (encompassing 2733 patients), found that the addition of an agent against EGFR to gemcitabine-based chemotherapy improved overall and progression-free survival compared with gemcitabine-based chemotherapy alone in patients with pancreatic cancer.[20] However, they found no benefit of adding anti-VEGF agents gemcitabine-based chemotherapy in overall survival or progression-free survival.

Ko et al (2012) performed a phase 2 study (N = 61) which assessed the efficacy and safety of bevacizumab plus cetuximab with or without gemcitabine in patients with advanced pancreatic cancer.[11] Patients with locally advanced or metastatic pancreatic cancer were randomized to receive cetuximab (400 mg/m^2 initially then 250 mg/m^2 weekly) plus bevacizumab (10 mg/kg every two weeks) either with or without gemcitabine (1000 mg/m^2 weekly 3 out of 4 weeks). Patients who received cetuximab, bevacizumab, and gemcitabine had longer median progression-free survival (3.53 months) and overall survival (5.41 months) than patients who only received cetuximab and bevacizumab (1.91 and 4.17 months, respectively). Both treatment regimens were well tolerated; however, patients who received gemcitabine had a greater frequency of grade 3–4 toxicities including thromboembolic events and proteinurea. The study was stopped because of the lack of efficacy in both treatment arms, and the authors concluded that the approach of inhibiting both EGFR/VEGF pathways in treating pancreatic cancer did not warrant additional studies.

In contrast to the findings of Ko et al, we found that the combination of cetuximab and bevacizumab increased progression-free survival and overall survival when added to conventional chemotherapy. The difference between the results of the two studies may reflect the different chemotherapy regimens used, as well as genetic differences between the Chinese population evaluated in our study and the population of the Ko et al study, which was performed in the United States. A larger sample size is necessary to further test the benefit of the combined VEGF/EGFR plus conventional therapy in treating patients with pancreatic cancer. Further studies should also explore if other chemotherapy regimens, other than the one used in this study, may affect outcomes.

Additionally, we searched the Taiwan National Health Insurance Database of the patients diagnosed with pancreatic cancer with conventional treatments between 2003 and 2009. With the exclusion of our 59 cases, 9611 subjects had overall survival rate of 0.015 for stage I plus stage II patients. No patient with unresectable (stage IV) pancreatic cancer survived up to 5 years.

The main limitation of this study is the nature of retrospective study with small numbers of patients. The limited size of the sample likely reflects the fact that pancreatic cancer is not as prevalent as other cancer types, such as breast cancer, colon cancer, and lung cancer. In our analysis, we include only ''pancreatic adenocarcinoma'' patients without other types of pathology in order to maintain patients' similar characteristics in the tumor morphology, grade, and other features of confounding. That may contribute a selection bias. However, the significant differences observed between the conventional and targeted therapies are likely meaningful, as the statistical analysis was rigorously performed. Less than 1 year survival was observed commonly for pancreatic carcinoma patients. The present study may provide supporting evidence that combination of two targeted medications (bevacizumab plus cetuximab) did improve the therapeutic response of pancreatic carcinoma patients.

In summary, our findings suggest an important benefit of this approach in treating advanced pancreatic cancer, and is one of the only few studies to show improved overall survival with treatment in patients with advanced pancreatic cancer. However, this benefit may be dependent upon the specific chemotherapy regimen that is used, as well as ethnic background. Future studies are warranted to further explore this therapeutic approach.

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
2. Bramhall SR, Allum WH, Jones AG, et al. Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. *Br J Surg.* 1995;82:111–115.

3. Nitecki SS, Sarr MG, Colby TV, et al. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann Surg.* 1995;221:59–66.
4. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *Am J Surg.* 1993;165:68–72; discussion 72–73.
5. Chang BW, Saif MW. Locally advanced pancreatic adenocarcinoma: where are we and where are we going? Highlights from the ''2011 ASCO Gastrointestinal Cancers Symposium.' San Francisco, CA, USA. January 20–22, 2011. *JOP.* 2011;12:101–105.
6. Teague A, Lim KH, Wang-Gillam A. Advanced pancreatic adenocarcinoma: a review of current treatment strategies and developing therapies. *Ther Adv Med Oncol.* 2015;7:68–84.
7. Sutton JM, Abbott DE. Neoadjuvant therapy for pancreas cancer: past lessons and future therapies. *World J Gastroenterol.* 2014;20: 15564–15579.
8. Li D, Xie K, Wolff R, et al. Pancreatic cancer. *Lancet.* 2004; 363:1049–1057.
9. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997;15:2403–2413.
10. Samore WR, Gondi CS. Brief overview of selected approaches in targeting pancreatic adenocarcinoma. *Expert Opin Investig Drugs.* 2014;23:793–807.
11. Ko AH, Youssoufian H, Gurtler J, et al. A phase II randomized study of cetuximab and bevacizumab alone or in combination with gemcitabine as first-line therapy for metastatic pancreatic adenocarcinoma. *Invest New Drugs.* 2012;30:1597–1606.
12. Burris H 3rd, Rocha-Lima C. New therapeutic directions for advanced pancreatic cancer: targeting the epidermal growth factor and vascular endothelial growth factor pathways. *Oncologist.* 2008;13:289–298.
13. Uegaki K, Nio Y, Inoue Y, et al. Clinicopathological significance of epidermal growth factor and its receptor in human pancreatic cancer. *Anticancer Res.* 1997;17:3841–3847.
14. Yamanaka Y, Friess H, Kobrin MS, et al. Coexpression of epidermal growth factor receptor and ligands in human pancreatic cancer is associated with enhanced tumor aggressiveness. *Anticancer Res.* 1993;13:565–569.
15. Oliveira-Cunha M, Hadfield KD, Siriwardena AK, et al. EGFR and KRAS mutational analysis and their correlation to survival in pancreatic and periampullary cancer. *Pancreas.* 2012;41:428–434.
16. Dittmann K, Mayer C, Fehrenbacher B, et al. Radiation-induced epidermal growth factor receptor nuclear import is linked to activation of DNA-dependent protein kinase. *J Biol Chem.* 2005;280:31182–31189.
17. Dittmann K, Mayer C, Fehrenbacher B, et al. Nuclear epidermal growth factor receptor modulates cellular radio-sensitivity by regulation of chromatin access. *Radiother Oncol.* 2011;99:317–322.
18. Dittmann K, Mayer C, Rodemann HP. Inhibition of radiation-induced EGFR nuclear import by C225 (Cetuximab) suppresses DNA-PK activity. *Radiother Oncol.* 2005;76:157–161.
19. Shah MA. The development of bevacizumab in noncolorectal gastrointestinal malignancies: gastroesophageal, pancreatic, and hepatocellular carcinoma. *Clin Adv Hematol Oncol.* 2014;12: 239–246.
20. Tian W, Ding W, Kim S, et al. Efficacy and safety profile of combining agents against epidermal growth factor receptor or vascular endothelium growth factor receptor with gemcitabine-based chemotherapy in patients with advanced pancreatic cancer: a meta-analysis. *Pancreatology.* 2013;13:415–422.
21. Bruns CJ, Harbison MT, Davis DW, et al. Epidermal growth factor receptor blockade with C225 plus gemcitabine results in regression of human pancreatic carcinoma growing orthotopically in nude mice by antiangiogenic mechanisms. *Clin Cancer Res.* 2000;6:1936–1948.
22. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205–216.