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

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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 and cisplatin, or 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.

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, irinotecan, 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. 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 gemcitabine-based chemotherapy alone. 8 Since the 1990s, gemcitabine has been the primary therapeutic agent for pancreatic cancer. 9 Current treatment regimens include 5-fluorouracil, leucovorin, oxaliplatin, irinotecan (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. 19 Over-expression of EGFR is associated with increased tumor aggressiveness and poor survival. 13–15 EGFR also promotes radioresistance by stimulating DNA repair by
ionizing radiation.\textsuperscript{16,17} Cetuximab (Erbitux\textsuperscript{8}; Bristol-Meyers Squibb, Lawrenceville, NJ) is an EGFR-specific chimeric IgG1 monoclonal antibody that inhibits EGFR-mediated signals transduction and radiation-induced repair.\textsuperscript{8,3} In addition, bevacizumab (Avastin\textsuperscript{10}; Genentech, South San Francisco, CA), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), inhibits tumor growth by inhibiting angiogenesis.\textsuperscript{19} Bevacizumab has demonstrated modest anti-pancreatic tumor activity but has not resulted in improvement in survival either alone or in combination with gemcitabine.\textsuperscript{19,20} Addition of cetuximab to gemcitabine did result in modest but statistically significant improvement in overall survival compared with gemcitabine therapy alone.\textsuperscript{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.\textsuperscript{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.\textsuperscript{13} 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.

\section*{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.

\subsection*{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\textsuperscript{3} and a platelet count $\geq$100,000/mm\textsuperscript{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.

\subsection*{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\textsuperscript{2} gemcitabine and 50 mg/m\textsuperscript{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\textsuperscript{2} cetuximab (at 350 mg/m\textsuperscript{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.\textsuperscript{22} Toxicities were evaluated using the common terminology criteria for adverse events (CTCAE) v4.

\subsection*{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., Armonk, NY), and the two-tailed $P$ value $<0.05$ was considered significant.

\subsection*{RESULTS}

\subsection*{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 $\sim$56 years. There was a greater percentage of males in the conventional compared with the targeted group (60.7% vs. 41.9%, respectively); however, this did not reach statistical significance ($P = 0.15$).

Time to disease progression was $\sim$10.7 months longer with targeted treatment compared with conventional therapy.
(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.

### 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.

### 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%)            |         |
| Neurological 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.

### 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 neurologic toxicities.
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 $\sim$9 months in those who received targeted treatment ($P < 0.001$) (Figure 1A). Longer progression-free survival was observed in the targeted treatment group compared with the conventional group for subjects aged $\leq 60$ 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 $\sim$7 months with conventional treatment and $\sim$10 months with targeted treatment for the entire population ($P = 0.003$) (Figure 1B). Similar to progression-free survival, targeted therapy was associated with longer overall survival than conventional therapy in patients $\leq 60$ 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 $\sim$6 months and extended overall survival by $\sim$3 months. The benefit for progression-free survival was independent of age, whereas the benefit for overall survival was primarily in patients aged $\leq 60$ 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.
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. However, most have shown disappointing results. 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 in overall survival or progression-free survival. They found no benefit of adding anti-VEGF agents gemcitabine or erlotinib to 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.

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