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Journal

American Journal of Clinical Oncology, 41(2)

ISSN

0277-3732

Authors

Davis, Elizabeth J
Griffith, Kent A
Kim, Edward J
et al.

Publication Date

2018-02-01

DOI

10.1097/coc.0000000000000240

Peer reviewed

HHS Public Access

Author manuscript

Am J Clin Oncol. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Am J Clin Oncol. 2018 February ; 41(2): 128–132. doi:10.1097/COC.0000000000000240.

A phase II study of biweekly cisplatin, fixed dose rate gemcitabine and infusional 5-fluorouracil in patients with metastatic pancreatic and biliary cancers

Elizabeth J. Davis, M.D.[1], **Kent A. Griffith, M.P.H. M.S.**[2], **Edward J. Kim, M.D., Ph.D.**[1], **Joshua M. Ruch, M.D.**[1], **Kevin J. McDonnell, M.D., Ph.D.**[1], and **Mark M. Zalupski, M.D.**[1]

[1] Department of Internal Medicine, University of Michigan, Ann Arbor, MI

[2] Department of Biostatistics, University of Michigan, Ann Arbor, MI

Abstract

Objectives—Combinations of gemcitabine, 5-fluorouracil (5-FU), and platinum have demonstrated improved outcomes compared with singlet chemotherapy in pancreatic and biliary cancers. This phase II study examined efficacy and safety of a novel schedule of cisplatin, fixed-dose-rate (FDR) gemcitabine and infusional 5-FU.

Methods—Patients with metastatic adenocarcinoma of the pancreas or biliary tract, previously untreated or having received one cytotoxic regimen for advanced disease, were treated with gemcitabine 1000 mg/m^2 intravenously (IV) over 100 minutes, cisplatin 35 mg/m^2 IV over 30 minutes and 5-FU 2400 mg/m^2 IV over 48 hours on day 1 of a 14 day cycle. Patients were treated until disease progression or for 12 cycles. After 12 cycles, patients with stable or responding disease could continue gemcitabine and 5-FU. The primary endpoint was objective response.

Results—Thirty-nine patients were treated: eight with biliary cancer (all untreated) and 31 with pancreatic cancer (17 untreated, 14 previously treated). Best response in 25 untreated patients was partial response (PR) in 40%, stable disease (SD) in 40% and progressive disease (PD) in 20%. In 14 previously treated pancreatic patients, best response was PR in 7%, SD in 50%, PD in 43%. Median overall survival in untreated patients was 10.3 months versus 4.9 months in previously treated patients. Adverse events were primarily uncomplicated hematologic toxicity, > grade 3 neutropenia (54%), anemia (21%) and thrombocytopenia (13%).

Conclusions—Biweekly cisplatin, FDR gemcitabine, and infusional 5-FU demonstrated a high response rate and was well-tolerated, encouraging further investigation of this regimen in metastatic pancreatic and biliary cancers.

Keywords

metastatic pancreatic cancer; metastatic biliary cancer; gemcitabine; cisplatin; 5-fluorouracil

Corresponding author: Mark M. Zalupski, M.D., Professor, Department of Internal Medicine, Division of Hematology-Oncology, University of Michigan, Ann Arbor, MI, 1500 E. Medical Center Dr., Ann Arbor, MI 48109, 734-615- 3969, 734-647- 9647, Zalupski@.umich.edu.

Introduction

In 2015, more than 50,000 cases and 40,000 deaths will occur in the United States from pancreatic and biliary cancers. Most patients with either disease present at an advanced stage with resultant poor prognosis and median survival of less than one year (1).

Gemcitabine and 5-fluorouracil (5-FU), alone or in combination with cisplatin, have demonstrated clinical efficacy in both diseases. In advanced biliary cancer, the combination of gemcitabine and cisplatin as compared to single agent gemcitabine, demonstrated an improvement in survival (OS) (11.7 vs. 8.1 months, $p< 0.001$) and progression-free survival (PFS) (8 vs. 5 months $p<0.001$) (2). In pancreatic cancer, a meta-analysis of phase III trials comparing gemcitabine alone to gemcitabine with a platinum or capecitabine, demonstrated improved survival with combination therapy (3). In most trials in pancreatic cancer, doublet therapy is also associated with improved response rates and progression free survival and is reasonably tolerable.

Recently, two phase III trials in pancreatic cancer demonstrated efficacy for novel chemotherapy combinations (4, 5). FOLFIRINOX, a combination of 5-FU, irinotecan and oxaliplatin, was compared to gemcitabine alone in patients with previously untreated, metastatic pancreatic cancer. Those treated with FOLFIRINOX had improvements in median OS (11.1 vs. 6.8 months), median PFS (6.4 vs. 3.3 months), and response rate (31.6 vs. 9.4%). Grade 3/ 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy were also significantly higher in the FOLFIRINOX group (4). In a second study in patients with metastatic pancreatic cancer, nab-paclitaxel in combination with gemcitabine demonstrated improved OS (8.5 vs. 6.7 months), PFS (5.5 vs. 3.7 months), and response rate (23 vs. 7%) as compared with gemcitabine alone (5). While these results support the use of combination chemotherapy in fit patients with adequate performance status, toxicity considerations necessitate ongoing studies to define regimens with comparable or greater efficacy and less toxicity.

We previously reported two phase II trials in pancreatic cancer incorporating infusional 5-FU into a combination treatment regimen (6, 7). The first added a 21 day infusion of 5-FU to weekly gemcitabine and biweekly cisplatin. In 31 previously untreated patients with metastatic pancreas cancer, the response rate was 26% with a median duration of 7.1 months and median survival of 8.5 months (6). A more recent trial added a 48 hour infusion of 5-FU to biweekly gemcitabine delivered by fixed-dose-rate (FDR) infusion with bevacizumab (6). In 42 previously untreated patients, response rate was 30%, median PFS 5.9 months and median OS 7.4 months (7). In this second trial, chemotherapy was especially well-tolerated with little need for treatment delay or dose reduction. In response to these experiences, further investigation of a regimen utilizing biweekly cisplatin, FDR gemcitabine, and 48 hour infusional 5-FU in previously untreated and treated patients with advanced pancreatic and biliary cancers was conducted and is reported here.

Materials and Methods

Eligibility

Patients with a pathologic diagnosis of pancreatic adenocarcinoma or biliary tract cancer and clinical or radiological evidence of metastatic disease were eligible for this study. For the previously untreated strata, no prior therapy for metastatic disease was allowed and previous adjuvant treatment or therapy for locally advanced disease must have been completed more than 6 months prior to study entry. In the previously treated cohort, systemic therapy for metastatic disease was limited to one cytotoxic chemotherapy regimen not containing cisplatin. Prior gemcitabine or infusional 5-FU was allowed but not both agents. Patients treated with (neo)adjuvant chemotherapy for resectable, resected or unresectable disease recurring or progressing within 6 months of treatment completion were eligible for the once treated strata provided their previous therapy did not include cisplatin or gemcitabine and infusional 5-FU. Participants were required to have an ECOG performance status 0-1, and to have adequate hematologic (absolute neutrophil count >1,500/mm3, platelet count >100,000/mm3, renal (serum creatinine <1.25 × ULN) and hepatic function (total bilirubin < 3.0 mg/dl with relief of biliary obstruction by endobiliary stent or a percutaneous transhepatic cholangiography (PTC) tube). At least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was required. Patients with serious concomitant medical disorders or pre-existing peripheral neuropathy > grade 2 were excluded. Previous malignancies treated with curative intent and with no evidence of recurrence were permitted. This study was approved by the University of Michigan Institutional Review Board, and all patients provided written informed consent prior to treatment. The trial is registered with ClinicalTrials.gov, number NCT01661114.

Treatment Plan

Baseline history, physical examination, complete blood count (cbc), serum chemistry, CA 19-9, and a computed tomography (CT) scan of the chest, abdomen, and pelvis were obtained within 2 weeks of starting protocol therapy. A cbc was obtained weekly during cycles 1 and 2 then every cycle. Serum chemistry was obtained every cycle. A history / physical exam, and CA 19-9 were obtained every 2 cycles. CT scan for response assessment using the RECIST version 1.1 was performed every 4 cycles.

Treatment was given in the outpatient setting and included gemcitabine 1000 mg/m^2 intravenously (IV) over 100 minutes on day 1, cisplatin 35 mg/m^2 IV over 30 minutes on day 1 and 5-FU 2400 mg/m^2 IV over 48 hours beginning day 1 of a 14 day cycle. Patients were treated until disease progression, inter-current illness, unacceptable toxicities despite dose modifications, or patient decision to withdraw from the study treatment. Following 12 cycles of therapy with stable or responding disease, patients could stop therapy and be observed or continue therapy with gemcitabine and infusional 5-FU only.

Dose modifications were made based on toxicities experienced in the preceeding cycle and on the day treatment was due. All toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. A cycle of therapy could begin when the absolute neutrophil count (ANC) ≥ 1,000/mm3, platelets ≥ 75,000/ mm3, and all other

treatment related toxicity had resolved to ≤ grade 1. For febrile neutropenia or if the ANC < 1000/mm3 or platelets < 75,000/mm3, chemotherapy was held and counts were evaluated weekly. Treatment resumed upon recovery to an ANC > 1000/mm3 and platelets > 75,000/mm3, with gemcitabine and cisplatin dose reduced by 20%. If gastrointestinal (GI) toxicity occurred during febrile neutropenia, 5-FU was also dose reduced by 20%. For grade 2-3 diarrhea or mucositis, chemotherapy was held and at resolution of toxicity to ≤ grade 1, 5-FU was dose reduced 20%. Grade 4 diarrhea or mucositis required a 40% dose reduction of 5FU. Cisplatin was held for ≥ grade 2 neuropathy and could be resumed with a 20% dose reduction if toxicity resolved to ≤grade 1. If creatinine increased > 1.25 × ULN, cisplatin was held; cisplatin could be resumed at a 20% dose reduction if creatinine improved to < 1.25 × ULN. Agent(s) were permanently discontinued if more than 3 dose reductions for toxicity were needed. An agent(s) could be discontinued and protocol therapy continued with remaining agents.

Statistical design and analysis

This was a single center, phase II trial conducted at the University of Michigan. The trial used a Minimax Simon two-stage design for previously untreated patients. For the first stage, up to 15 patients were accrued with at least 2 objective responses needed to continue to the second stage of 10 additional patients, for a total stratum of 25 patients. A single stage design for previously treated patients was employed, requiring a sample size of 14 patients. The primary endpoint for both strata was best objective response. All patients receiving any protocol therapy were considered evaluable for the primary endpoint; patients not receiving 4-cycles and response assessment were considered treatment failures. Patients were stratified based upon previous treatment but not by primary disease. Objective response was measured after every 4th cycle of treatment. The best overall response was defined as the best response recorded from the start of the treatment until disease progression/recurrence. The duration of response was measured from when complete response (CR) or partial response (PR) (whichever was first) when recorded until the first date that recurrent or progressive disease was objectively documented. Secondary endpoints were progression free survival (PFS), overall survival (OS), tolerability, and toxicity.

In previously untreated patients, we hypothesized that this triplet regimen would be of interest if best objective response was at least 30%. In previously treated patients, we defined a response rate of further interest as at least 20%. For both strata, the design provided for at least 80% power to detect our hypothesized differences in objective response rates, with at most a 5% type I error.

Results

Patient characteristics

Between July 2011 and December 2013, thirty-nine eligible patients were enrolled and treated and are included in this report. Patient characteristics are listed in Table 1. Eight patients had biliary cancer (all in the previously untreated cohort), and 31 patients had pancreatic cancer. Twenty-two patients had received no prior therapy, and 17 patients had been treated previously, 3 in the localized setting, 14 for advanced disease. Prior treatment in

advanced disease included FOLFIRINOX (n=8), gemcitabine (n=3) and gemcitabine combinations (n=3). All patients had metastatic disease; in the previously untreated group (n=25) sites of involvement included liver (56%), lung/lymph nodes (40%), peritoneal cavity (28%) and in those previously treated (n=14), liver (64%), lung (50%), and peritoneal cavity (50%).

Treatment administration

Patients received a total of 338 treatment cycles. The median number of cycles in the previously untreated cohort was 12 (1-25) and in previously treated patients 5 (3-12). All patients received at least one full cycle of treatment and 97% of patients received at least 2 cycles of therapy. Three patients required dose reduction of all three agents for cycles 2 or 3. Per protocol dose reductions for cycles 2 and 3 were required for gemcitabine in 5% and 21% of patients, for cisplatin in 18% and 26% of patients, and for 5FU in 10% and 8% of patients, respectively. Treatment was given without delay in 90% patients for cycle 2 and for all patients in cycle 3. Six patients continued protocol therapy beyond cycle 12 with gemcitabine / 5FU only, for a median of 4 additional cycles.

Response to treatment and survival

In the previously untreated cohort (n=25), best response to therapy was partial response in 10 (40.0% 95 CI 21.1-61.3), stable disease in 10 (40.0% 95% CI 21.1-61.3) and progressive disease in 5 (20.0% 95% CI 6.8 –40.7), including 2 patients who were not evaluated for response and were considered treatment failures (Table 2). Response rates in previously untreated patients with pancreatic cancer (n=17) and biliary cancer (n=8) were 41.2% (95% CI 18.4-67.1) and 37.5% (95% CI 8.5-75.5), respectively. Median duration of response in those with PR was 5.9 months (range 1.2-13.8). Median PFS was 5.6 months (95% CI 3.7-7.2, range 1.5-15.7) and marginally longer in biliary as compared to pancreatic patients (7.7 vs. 5.6, p=0.13). Disease control rates following 4, 8 and 12 cycles of therapy were 80%, 52% and 36%, respectively.

In the previously treated cohort (n=14), all patients with advanced pancreatic cancer, the best response to therapy was partial response in one (7.1% 95% CI 0.2-33.9) lasting 5.3 months, stable disease in 7 (50.0% 95% CI 23.0-77.0), and progressive disease in 6 (42.9%, 95% CI 17.7-71.1). Median PFS was 2.7 months (95% CI 1.8-4.5; range 1.6-8.5). Disease control rates following 4, 8 and 12 cycles of therapy were 50%, 29% and 21%, respectively.

Twelve patients had disease control through 12 cycles of therapy, with 6 electing observation and 6 continuing therapy with gemcitabine and 5FU only. The median number of cycles received beyond 12 in those continuing therapy was 4 (range 2-12) with median PFS of 9.7 months from treatment start (range 6.7-13.7). In those electing observation, median PFS from treatment start was 8.3 months (range 7.0-15.7), p=NS for comparison between groups.

Five patients are still living in the previously untreated cohort and 2 in the previously treated group. With data censored on August 1, 2014, median survival in the previously untreated cohort is 10.3 months (95% CI 8.0-19.4; range 2.1-31.2+). Patients with biliary cancer had a median OS of 15.6 months (2.1 – 31.2+) and those with pancreatic cancer had a median OS of 9.1 months (95% CI 6.9-16.4; range 2.1-27.1). Previously treated patients had a median

OS of 4.9 months (95% CI 3.6-11.9; range 3.0-14.2+). Survival is depicted graphically in figure 1.

Significant univariate associations between patient, disease and response characteristics and OS were explored. Covariates of interest were patient's gender, ECOG performance status, CA19-9 level at baseline and after 2 cycles of therapy and the change between the two, primary site of disease (pancreatic vs. biliary), site and number of sites of metastatic disease (1 vs. > 1, liver, lung/lymph node, peritoneal cavity), and previous treatment for metastatic disease (per eligibility criteria for previous treated and previously untreated patients). OS was not significantly associated with gender (p=0.72), baseline CA19-9 (p=0.23) or site of metastasis (liver p=0.11, peritoneal p=0.13, lung/lymph nodes p=0.32). In this population, OS was marginally associated with ECOG performance status (p=0.101), primary disease site (p=0.094) and one vs. > 1 site of metastasis (p=0.058). OS was significantly associated with no previous treatment for metastatic disease (p=0.0096) and CA19-9 levels after 2 cycles of therapy (p=0.0276) and similarly to worsening CA19-9 (p=0.0134) after 2 cycles of therapy compared to baseline (Figure 2).

Toxicity

Toxicities are summarized in Table 3. Most events were grade 1 or 2. The most common severe toxicities were hematologic which occurred equally frequently between treatment strata. Grade ≥ 3 neutropenia occurred in 52% of previously untreated and 57% of previously treated patients although, somewhat surprisingly, there were no instances of neutropenic fever or neutropenic infection in either population. Nine patients experienced a grade 4 event; 8 were hematologic, one was gastrointestinal. There were no grade 5 events. The most common non-hematologic adverse events in both cohorts were GI toxicities (anorexia, nausea/vomiting, diarrhea) and fatigue.

During the course of study treatment, seventeen patients (44%) experienced 20 hospitalizations, 14 in the previously untreated cohort and 6 in previously treated patients. When considering cohort size and median time on therapy, 4.1 vs. 2.7 months for previously untreated and previously treated patients, respectively, the hospitalization rate was comparable between cohorts. Fifty percent of hospitalizations were at least possibly related to treatment per investigator attribution.

Discussion

Multi-agent chemotherapy has been demonstrated to be superior to single agent treatment in both pancreatic and biliary carcinomas. We report a single center, phase II trial of a tolerable triplet chemotherapy regimen in patients with metastatic pancreatic or biliary cancer, one cohort previously untreated and a second smaller group of previously treated patients. In treatment naïve patients, this regimen demonstrated high response and disease control rates. We hypothesized that a response rate of at least 30% in previously untreated patients would be of interest; a 40% partial response rate was observed (41% of pancreatic patients, 37% of biliary patients). Notably, the median PFS and OS were comparable to more intensive regimens. Our results are similar to two other published phase II studies using the gemcitabine, 5-fluorouracil, and cisplatin regimen in a total of 59 patients with advanced or

metastatic biliary cancer (8,9). Those studies reported response rates of 32 and 33.3% and median overall survivals of 11.2 and 18.8 months, comparable to the 15.6 months seen in this study. Toxicities in both of these trials were primarily hematologic, similar to our study.

Results in previously treated pancreatic cancer patients were not as impressive, which might be expected as a majority of this cohort had progressed on FOLFIRINOX or gemcitabine combinations. In this group of patients, we set 20% response as a clinically meaningful target. Although only one response was observed (7% response rate), therapy was well tolerated and 5 patients survived at least 6 months (36%) and 2 (14%) beyond one year.

Outcomes for patients with pancreatic cancer have improved with the development of FOLFIRINOX and the approval of the gemcitabine/nab-paclitaxel combination. Despite these advances, there is concern regarding the toxicity of therapy. With the introduction of FOLFIRINOX, we performed a retrospective study to evaluate efficacy and tolerance in an initial 54 patient cohort treated in 3 institutions (10). While a 39% partial response rate and 29% stable disease rate were observed, median PFS and OS of 3.8 and 7.2 months were not particularly impressive. Furthermore, 61% of patients experienced toxicity of at least grade 3 and 87% of patients required dose reductions. Most revealing, 35% of the patients discontinued therapy due to toxicity. Similar experience in many centers has prompted modification of FOLFIRINOX, with omission of 5FU bolus +/− leucovorin, and arbitrary dose reductions of irinotecan and/or oxaliplatin. The gemcitabine and nab-paclitaxel combination is suggested to be better tolerated than FOLFIRINOX although myelosuppression is common, and fatigue, myalgias, arthralgias and neuropathy are often treatment limiting. In this current study, while toxicity rates appeared similar to FOLFIRINOX and/or gemcitabine / nab-paclitaxel, this was in part a function of weekly blood counts in cycles 1 and 2, documenting clinically insignificant neutropenia/leukopenia. Myeloid growth factors were not used. Protocol specific dose reductions led to continuing therapy with good tolerance. There were no instances of neutropenic fever or infection, and no study patient discontinued therapy secondary to toxicity.

If chemotherapy combinations of 2-3 cytotoxic agents have similar efficacy in pancreatic and biliary cancers, regimens with less toxicity and/or less expense might be favored. The drug costs of one month of therapy, including those provided as supportive measures in our center, were calculated for the study regimen, FOLFIRINOX and gemcitabine/nab-paclitaxel (Table 4). While appreciating that practices vary, especially as to use of anti-emetics and growth factors, the cost differences between regimens are considerable.

The gemcitabine, docetaxel, and capecitabine combination (GTX) has been reported to be active in pancreatic cancer and tolerable in older patients or those with poorer performance status (11, 12). More recently, a 4 drug combination of GTX and low dose cisplatin was reported to result in a response rate of 50% and a median survival of more than 12 months in 29 patients with previously untreated metastatic pancreatic cancer (13). These regimens, like our study regimen, utilize gemcitabine by FDR infusion and lower doses of chemotherapy, taking advantage of clinically recognized synergism between cisplatin, gemcitabine and fluoropyrimidine agents. The intensity and toxicity of treatment appear less than with more standard regimens. These results speak to the importance of continued and expanded

evaluation of multi-agent chemotherapy beyond FOLFIRINOX and gemcitabine/nab-paclitaxel in the treatment of pancreatic (and biliary) cancer.

In summary, like FOLFIRINOX, this study regimen utilizes 3 cytotoxic agents and is given every 2 weeks. It substitutes FDR-gemcitabine for irinotecan, with single agent activity and tolerance favoring gemcitabine. The study regimen incorporates principles of combination chemotherapy with an emphasis on non-overlapping toxicities. The chemotherapy combination of biweekly cisplatin, infusional 5FU and FDR-gemcitabine is tolerable and active in pancreatic and biliary cancers and is appropriate for expanded evaluation and use in these diseases.

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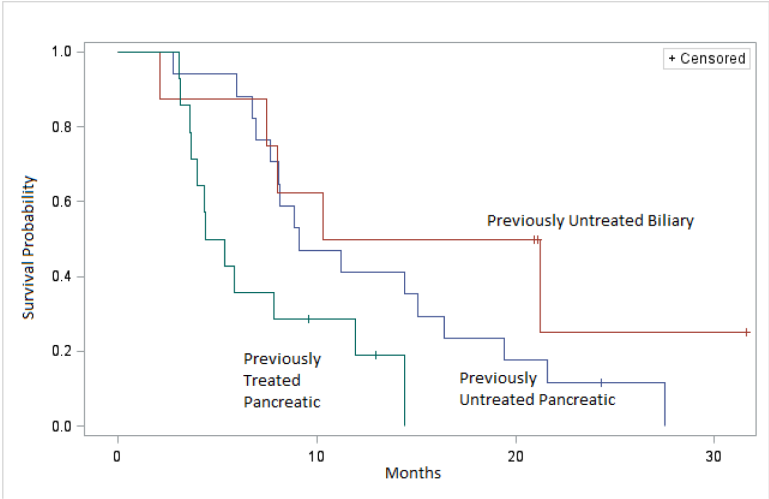

Figure 1.

Red- previously untreated biliary

Blue- previously untreated pancreatic

Green- previously treated pancreatic

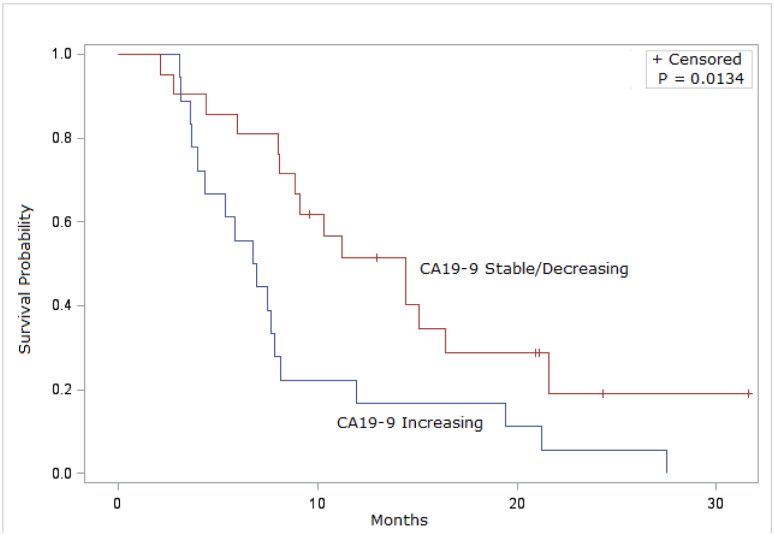

Figure 2.

Red- CA 19-9 stable/decreasing

Blue- CA 9-9 increasing

Table 1

Patient characteristics

Characteristic	Previously untreated		Previously treated
	Pancreas	Biliary	Pancreas
Number of patients	17	8	14
Mean age in years (range)	59 (34-75)	61 (25-80)	64 (49-75)
Gender			
Women	9	4	3
Men	8	4	11
Race			
White	16	7	14
Black	1	1	0
ECOG Performance status			
0	7	3	5
1	10	5	9
Baseline CA 19-9 (range)	96,624 (4-904,348)	2,733 (4-18,118)	2,822 (2-18,903)
Site of metastatic disease			
Lung/LN	5	5	7
Liver	8	6	9
Peritoneum	6	1	7

Table 2

Response by RECIST 1.1

Best overall response	Previously untreated		Previously treated
	Pancreas	Biliary	Pancreas
Complete response	0	0	0
Partial response	7	3	1
Stable disease	7	3	7
Progressive disease	3	2	6

Table 3

Worst toxicity experienced per patient

Toxicity	Previously untreated n=25		Previously treated n=14	
	Any AE (%)	AE ≥ grade 3 (%)	Any AE (%)	AE ≥ grade 3 (%)
Hematologic				
Hemoglobin	84	20	71	21
Platelets	80	12	64	14
Neutrophils	64	52	79	57
Non-hematologic				
GI	72	24	57	7
Fatigue	52	0	36	0
Metabolic derangement	40	4	7	0
Neuropathy	28	0	7	0
VTE	20	8	14	7
LFT abnormalities	16	4	7	0
Renal	12	0	14	0
Fever	12	0	7	0
Infection	12	0	7	7
Endocrine	12	0	0	0
Syncope	0	0	7	7

Table 4

Drug costs by regimen

Regimen	Antiemetics*	Cost (in U.S. dollars)	g-csf**
5-FU, Cisplatin, & Gemcitabine	dexamethasone, palonosetron	5,530.33	none
FOLFIRINOX	dexamethasone, palonosetron, fosaprepitant	9,982.64	~ 50%
Gemcitabine & nab-paclitaxel	dexamethasone, ondansetron	27, 226.68	optional

For 1 month of therapy based on patient with BSA of 2.0 m^2

*Antiemetics – dexamethasone 8 mg IV/8 mg po, palonosetron 0.25 mg IV, fosaprepitant 150 mg IV, ondansetron 8 mg po

**myeloid growth factors – neupogen for 10 days adds $15,866.90 per month