Gemcitabine, irinotecan and celecoxib in patients with biliary cancer

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The incidence of hepatobiliary cancers is increasing and no standard therapy currently exists. Gemcitabine is an active drug in this disease. Previous studies suggest that the combination of gemcitabine and irinotecan is active with reasonable toxicity profiles in pancreatic and hepatobiliary cancers. COX-2 induction and overexpression have been documented in biliary dysplasia and biliary malignancies. We report on a case series of the efficacy and toxicity of gemcitabine plus irinotecan plus celecoxib in patients with advanced biliary cancer. The treatment consisted of gemcitabine 1000 mg/m^2 given intravenously on days 1 and 8, irinotecan 100 mg/m^2 given intravenously on days 1 and 8, and celecoxib 400 mg orally twice daily every 21 days. Six patients were enrolled, one was ineligible, therefore data were examined on the five remaining patients. One patient had a complete response, one had a partial response, two had stable disease, and one received one cycle of treatment and decided on surgery hence could not be assessed. The treatment was well tolerated with one grade 4 adverse event of thrombocytopenia. In conclusion, the combination of gemcitabine, irinotecan, and celecoxib appears to be well tolerated with some activity against biliary cancer. Further studies using this combination are warranted. *Anti-Cancer Drugs* **20:294–300 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The incidence of biliary cancers is increasing and 5-year survival of all biliary cancers is less than 5% with median survival of less than 1 year [1]. In 2008, it is estimated that there will be approximately 9500 new cases of gallbladder and other extrahepatic bile duct cancers and approximately 19 160 intrahepatic bile duct and liver cancers diagnosed in the United States [2]. More than 90% of patients die of their disease, accounting for approximately 2% of American cancer deaths. Long-term survival is highly dependent on the effectiveness of surgical therapy. Surgical resection offers the only hope of cure [3]. For patients with unresectable or metastatic disease, there is no hope for long-term control of disease with death occurring within 6 months to a year from diagnosis [3–5]. Combinations of various chemotherapeutic agents have been tested with no one regimen providing any clear evidence of significant response or benefit. To date, there is no accepted standard regimen for treatment of these diseases [6–9]. Recent reports in phase I and II trials suggest a greater response rate for combinations of 5-fluorouracil (5-FU) or capecitabine and a platinum or gemcitabine combination with reported response rates of 20–40% [10–13]. Phase III trials have not been conducted to better study any combination of these agents. There is no accepted standard therapy for these diseases, therefore combinations of active drugs should be investigated.

On the basis of preclinical data suggesting a dose-dependent synergy between gemcitabine and irinotecan a phase I trial combining gemcitabine and irinotecan has been carried out [14–16]. The sequence of administration of gemcitabine followed by irinotecan, was empirical. No preclinical data were available to suggest sequence-related differences in toxicity or efficacy. The maximum tolerated dose of irinotecan given intravenously (i.v.) over 90 min on days 1 and 8 every 3 weeks preceded by gemcitabine 1000 mg/m^2 given i.v. on days 1 and 8, was 100 mg/m^2/dose. Dose-limiting toxicity includes diarrhea at an irinotecan dose of 115 mg/m^2. The recommended phase II doses for this combination are gemcitabine 1000 mg/m^2 and irinotecan 100 mg/m^2 given on days 1 and 8 and repeated every 3 weeks as the starting dose. Escalation of irinotecan to 115 mg/m^2 may be considered for subsequent cycles in patients with minimal or no toxicity during the first cycle. This phase I experience included three patients with previously untreated advanced pancreatic cancer [15]. Two of the three patients achieved documented partial responses (PRs). The third patient has had a clinical benefit response and shrinkage of measurable tumor not meeting PR criteria.

Cyclooxygenases regulate prostaglandin formation and has been shown to be involved in tumor development in multiple malignancies [17–25]. There are three isoforms

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of cyclooxygenase: COX-1, COX-2, and COX-3 [26]. The inducible isoform of cyclooxygenase, COX-2, is involved in tumor development and progression. Several studies have shown COX-2 induction in malignant tissues, but not in surrounding normal tissues [17–20,26]. COX-1 is present in most cells, unlike COX-2 which is only found in normal liver, kidney, and pancreatic island tissue. COX-2 induction has been found in hepatobiliary cancers [27–34]. A recent study by Schmitz *et al.* [24] found that increased COX-2 expression was correlated with decreased apoptosis and increased tumor proliferation. Patients with strong COX-2 expression had significantly lower overall survival versus those with COX-2 negative expression (11.4 vs. 22.8 months). Santini *et al.* [31] found that COX-2 overexpression in surgically resected ampullary cancer tissue was associated with decreased overall survival. Legan *et al.* [19] evaluated gallbladder tissue and found that the COX-2 expression is lowest in normal tissue and highest in high-grade dysplasia. Patients with normal or low-grade gallbladder dysplasia did not accumulate p53, but patients with high-grade dysplasia and adenocarcinoma accumulated p53. COX-2 overexpression was found in tissue with p53 accumulation more often than in tissue without p53 accumulation (94.4 vs. 40%, $P < 0.0001$) [19]. COX-2 expression is important because it offers an alternate target using NSAIDs, such as COX-2 inhibitors. Celecoxib (400 mg twice daily) decreases polyp formation in patients with familial adenomatous polyposis [35,36]. In-vivo studies have shown that COX-2 selective inhibitors have antitumor activity with growth inhibition of Lewis lung tumors, HT-29 colon cancer, head and neck cancer, skin cancer, and bladder cancer [21–23,25]. Current data suggest that COX-2 activity is important for angiogenesis, tumor growth, and metastases.

A phase II trial using gemcitabine plus irinotecan plus celecoxib was initiated to assess the activity of this regimen in patients with biliary cancer by measuring response rate, time to progression, and overall survival.

Patients and methods

This is a single-center, nonrandomized, phase II study. The study was approved by the institution's review board and all patients signed informed consent.

Patient population

Patients with previously untreated, unresectable, recurrent or metastatic gall bladder, or bile duct carcinoma who met eligibility criteria were included for this study. Neoadjuvant chemotherapy and/or radiation therapy was allowed at the time of initial diagnosis with localized disease. Prior treatment with gemcitabine and/or irinotecan was not allowed. Prior thoraco-abdominal surgery was allowed if it was more than 3 weeks prior to registration and the patient recovered completely. Other inclusion criteria were Zubrod performance status 0–2, pretreatment labs as follows: granulocyte count $> 1500/\mu l$, platelet count $\geq 100\,000/\mu l$, serum creatinine $\leq 1.5 \times$ the institutional upper limit of normal, bilirubin of $\leq 2 \times$ the institutional upper limit of normal, serum glutamic oxaloacetic transaminase less than $5 \times$ the institutional upper limit of normal.

Exclusion criteria were: active inflammatory bowel disease, significant bowel obstruction, chronic diarrhea, known brain metastases (no imaging required), unstable comorbid conditions, pregnant women, nursing women, patients of reproductive age unless they agreed to use effective contraceptives. There should have been no plan for concomitant radiation therapy, hormonal therapy, or other chemotherapy for their tumor.

Treatment plan and dose modification

Gemcitabine 1000 mg/m^2 i.v. over 30 min was given on days 1 and 8, every 21 days. Irinotecan 100 mg/m^2 i.v. over 90 min was given on days 1 and 8, every 21 days. Celecoxib 400 mg orally twice daily was given continuously during the study. Gemcitabine was given before irinotecan. Patients were continued on this regimen until disease progression, unacceptable toxicity, treatment delay greater than 2 weeks, or patient decision to withdraw from the study. The plan was to continue treatment for at least six cycles for patients achieving complete response (CR), PR, or stable disease (SD). Before treatment with gemcitabine and irinotecan the following premedications were given: dexamethasone 10 mg i.v. (antiemetic) and either ondansetron or granisetron or dolasetron. Lorazepam 1–2 mg i.v./orally was given if needed before irinotecan. No prophylactic anticholinergic medications were given. Loperamide 4 mg every 4 h was used as needed for treatment-related diarrhea. Granulocyte macrophage-colony stimulating factor (sargramostim) was not allowed. Prophylactic use of granulocyte-colony stimulating factor was not recommended, but was allowed for patients experiencing severe neutropenic complications and used as per accepted guidelines.

Dosage modifications

If there were multiple drug toxicities, the toxicity requiring the greatest dose reduction was used. Dose modifications

Table 1 Dose modification steps

	Dose			
Drug	Starting	Level-1	Level-2	Level-3
Irinotecan (mg/m^2)	100	75	50	Remove from trial
Gemcitabine (mg/m^2)	1000	750	500	Remove from trial
Celcoxib (mg, b.i.d.)[a]	400	200	100	Remove from trial

b.i.d., twice daily.
[a]If baseline liver function was abnormal, the starting dose was reduced to 50%.

for gemcitabine and irinotecan were used for abnormal liver function tests. Once a dose modification was made, there was no escalation of dose later. Recommended dose modification is listed in Table 1.

Day 1 dose modifications

These modifications were based on the worst toxicity experienced during the prior cycle, the same dose was given on day 8 unless criteria in the next paragraph prompted further dose reduction. Gemcitabine and irinotecan were dose reduced one level for febrile neutropenia, sepsis, thrombocytopenia requiring transfusion, grade 4 stomatitis/esophageal/dysphagia, or for other grade 3 or greater nonhematologic toxicities not listed in this paragraph. Gemcitabine was dose reduced one level for grade 2 or greater stomatitis/esophageal/dysphagia and for grade 3 or greater edema. Irinotecan was dose reduced one level for grade 3 or greater diarrhea and grade 2 pulmonary toxicity. Gemcitabine and irinotecan were discontinued for grade 3 or greater pulmonary toxicity. Gemcitabine was discontinued for grade 4 skin toxicity and grade 2 or greater pulmonary toxicity.

Day 8 dose modifications

These modifications were based on the worst toxicity during the current cycle on day 8. For gemcitabine and irinotecan, a one level dose reduction was performed for absolute neutrophil count 1000–1499 or platelet count of 75 000–99 000. Gemcitabine and irinotecan were not given on day 8 for absolute neutrophil count less than 1000, platelet count less than 75 000, febrile neutropenia, sepsis, thrombocytopenia requiring transfusion, or other nonhematologic toxicity grade 2 or greater. Gemcitabine and irinotecan were discontinued for grade 3 or higher pulmonary toxicity. Gemcitabine was dose reduced one level for grade 3 or greater skin toxicity. Gemcitabine was not given for grade 2 or greater stomatitis or esphogeal/dysphagia, or grade 3 or greater edema. Irinotecan was dose reduced one level for grade 2 diarrhea and was not given for grade 3 or greater diarrhea.

Celecoxib dose reductions

Celecoxib doses were reduced one level for platelet count of 50 000–99 000, grade 2 bilirubin/aspartate aminotransferase (AST)/alanine aminotransferase (ALT), or for grade 1 renal toxicity. Celecoxib doses were reduced two levels if both bilirubin and AST or ALT were grade 2. Celecoxib was held for platelet count less than 50 000, thrombocytopenia requiring transfusion, grade 2 or greater gastrointestinal ulceration, grade 3 or higher diarrhea, grade 3 or greater stomatitis/esophageal/dysphagia, grade 3 or greater bilirubin, AST/ALT, grade 2 or greater renal toxicity, or for other grade 3 or greater nonhematologic toxicity. In the event of any cerebrovascular or cardiovascular event, celecoxib was discontinued.

Before each cycle, the following were required: granulocyte count greater than 1500/mm^3, platelet count greater than 100 000/mm^3, and any treatment-related diarrhea had to be fully controlled. Any toxicity had to be less or equal to grade 1 before proceeding with additional treatment. Treatment evaluation was made weekly. If treatment was withheld for more than 2 weeks, the patient was excluded from the study.

Response and toxicity assessment

Response was assessed using the Response Evaluation Criteria in Solid Tumors [37]. To achieve CR or PR, patients had to maintain CR or PR at two different assessments that were at least 4 weeks apart. Disease progression was considered to be any progression within 12 weeks of study registration. Toxicity of adverse events and laboratory abnormalities were assessed and graded according to the National Cancer Institute-Common Toxicity Criteria 2.0.

Statistical analysis

The study was designed to evaluate the response rate, duration of survival, duration of response, and overall survival. The primary end point was response rate. The secondary end points were time to progression, overall survival, and toxicity. Patient baseline characteristics were tabulated using descriptive statistics. However, given the limited enrollment, we can only descriptively summarize the results of this study. Baseline characteristics for each individual patient are given in Table 2 and include age at enrollment, sex, race, ethnicity, disease status at enrollment, histology, and performance status. Treatment outcome summary for each patient is given in Table 3 and include number of cycles completed, best response, time to progression, survival time, and reason taken off treatment. Time to progression was measured from the date of study registration to the day of disease progression or death because of any cause. Time to death was measured from the date of study registration to the date of death because of any cause. Table 4 summarized the

Table 2 Baseline characteristics

Age (years)	Sex	Race	Ethnicity	Current disease	Histology	Performance status
65	Male	Caucasian	Non-Hispanic	Metastatic (liver)	Adenocarcinoma	0
64	Male	Caucasian	Non-Hispanic	Regional (bile duct involving pancreas)	Adenocarcinoma	1
68	Female	Asian	Non-Hispanic	Metastatic (liver)	Adenocarcinoma	1
56	Female	Caucasian	Non-Hispanic	Metastatic (liver)	Adenocarcinoma	1
59	Female	Caucasian	Non-Hispanic	Regional (gall bladder), metastatic (liver)	Adenocarcinoma	1

Table 3 Treatment and outcome summary

Patient	Number of cycles completed	Best response	Time to progression (months)[a]	Survival time (months)	Reason taken off treatment
1	4	CR	10.4	21.9	Patient's request
2	7	SD	27.3	27.3	Unacceptable toxicity
4	6	SD	9.8	12.3	Unacceptable toxicity
5	1	Unable to assess	12.5	17.0	Patient's request – had one cycle of treatment then went for surgical resection
6	8	PR	6.4	6.4	>2-week delay beyond planned treatment

CR, complete response; PR, partial response; SD, stable disease.
[a]Time to progression is equal to survival time if patient had not had documented progressive disease before death.

Table 4 Toxicities experienced by each patient according to maximum grade

	Maximum grade (number of patients)			
Type of toxicity	1	2	3	4
Lymphatics		1		
Neurology		1		
Pain	2	2		
Dermatology	3	1	1	
Platelets	2	1		1
ANC/AGC		1	1	
Metabolic/laboratory			1	
Genitourinary/renal			1	
Cardiovascular			2	
Infection/febrile neutropenia			1	
Hepatic			1	
Gastrointestinal	2	2	1	
Hemoglobin	1	1	1	
Pulmonary		3		
Allergy/immunology	1			
Constitutional symptoms	1	2	1	

AGC, absolute granulocyte count; ANC, absolute neutrophil count.

maximum grade of adverse events for each patient based upon type of adverse event.

Results

Patient characteristics

The trial was started from 23 September 2003 to 27 August 2006 and was ended because of poor accrual. Our center enrolled 16 patients with cholangiocarcinoma and six patients with gallbladder carcinoma in that time period, but only six patients were potentially eligible for the trial. Patients with this disease frequently have liver function abnormalities that are too severe to be safely treated. One patient was not eligible as there was no pathologically confirmed diagnosis and the bilirubin was outside of the specified range. Five patients were eligible and evaluable for response. Patients ranged in age from 56 to 68 years, all had adenocarcinoma, and they all had a performance status of 0 or 1. Table 2 summarizes characteristics of the five patients. No statistical analysis was performed for the baseline characteristics, because of the small number of patients in this trial.

Response and survival

Patients completed between one and eight cycles of treatment. Best response to treatment was assessed for the four patients who completed more than one cycle of chemotherapy. One patient had a CR, one had a PR, and two patients had SD lasting 27 and 10 months, respectively. Chemotherapy was discontinued in two of the five patients who received six and seven cycles of treatment secondary to unacceptable cumulative toxicity. Time to progression and overall survival are summarized in Table 3.

Safety

One patient had a grade 4 thrombocytopenia. There were no other grade four toxicities (Table 4). Two of the five patients died because of disease progression, not because of toxicity while on the study protocol.

Discussion

The current treatment of unresectable or metastatic cholangiocarcinoma can include a combination of chemotherapy with radiation, chemotherapy using a 5-FU-based regimen or gemcitabine, (NCCN Practice Guidelines in Oncology v.2.2008), or palliative care only. It is important that we continue to explore new treatment options and combinations through the utilization of clinical trials.

We had poor accrual to the trial, therefore we are unable to draw conclusions with definite treatment implications. The results of these five patients show that the combination of gemcitabine, irinotecan, and celecoxib is tolerated with manageable toxicity. The results suggest some unknown degree of activity with two patients achieving objective responses and other two with prolonged SD. However, the precise figure cannot be determined. These data are no more reliable than that obtained from case reports, but do suggest some degree of activity. Our experience shows the difficulty in enrolling this group of patients into clinical trials, as only six of 22 patients enrolled to our institution were eligible for this trial. The primary reason for ineligibility was poor liver function, usually because of the patient's tumor or the underlying liver disease that predisposed the patient to this malignancy.

The treatment of advanced and metastatic biliary carcinoma is not well defined. The most commonly used regimens had been 5-FU based or combinations with response rates ranging from 0 to 15% and median survival of 2–12 months [6–9,38,39]. More recently, gemcitabine and gemcitabine-based regimens have shown response rates between 20 and 30% with median survival times between 5 and 12 months [11–13,40–42]. Four recent phase II trials of capecitabine and gemcitabine in patients with hepatobiliary tumors have shown response rates in

the range of 20–50% and median survival times of 12–14 months [1,43–45], suggesting that this combination may be more effective than older 5-FU-based regimens, however, no phase III trials are likely to be completed to answer this question. Serrano and Gerson [46] recently reported on an overall review of published trials of gemcitabine, alone or in combination, as a treatment for advanced biliary tract carcinoma. Gemcitabine monotherapy has been reported in 310 patients and gemcitabine-based combination therapy has been reported in 635 patients. Monotherapy with gemcitabine has response rates of 0–36% and overall survival of 4–14 months. Combination therapy with gemcitabine has response rates of 9.3–64% and overall survival of 4.7–18 months. The authors feel that treatment for biliary cancer should be a gemcitabine-based combination with a platinum or capecitabine or gemcitabine monotherapy. They concluded that gemcitabine monotherapy or gemacitabine-based combination therapy should be the standard of care for patients with advanced biliary tract cancer.

Others have evaluated regimens similar to ours, but to date, no definitive trials have been reported. Sun *et al.* [47], performed a phase I trial of fixed dose rate gemcitabine plus irinotecan in 32 patients with metastatic pancreatic or unresectable or metastatic biliary cancer. Two patients developed deep venous thrombosis. Dose-limiting toxicities included dehydration, diarrhea, fatigue, neutropenia, and neutropenic fever. There were two PRs observed in the nine patients with biliary cancer. Median overall survival was 7.0 months. Gemcitabine plus irinotecan was evaluated in 16 patients with locally advanced or metastatic biliary cancers by Bhargava *et al.* [48]. Two patients had a PR and six patients had SD for periods ranging from 4 to 11.5 months. Toxicity consisted of grade 3/4 neutropenia in seven patients with no episodes of febrile neutropenia, grade 3/4 thrombocytopenia in four patients, grade 3 diarrhea in two patients, and grade 3 nausea in one patient. Two patients died, one from disease progression and one from pneumonia. The authors concluded that the combination of gemcitabine plus irinotecan appears to possess modest clinical activity, and it is well tolerated in patients with advanced biliary cancer, however, patient accrual was continuing [48]. We have not found an updated report or published manuscript of the completed trial.

A preliminary report of the combination of gemcitabine, irinotecan, and celecoxib has been reported in 11 patients with unresectable pancreatic cancer. The combination was noted to improve performance status, provide pain relief, and decrease levels of CEA and CA 19-9. Of the 11 patients, one had a partial response lasting 10 months, five had stable disease with duration ranging from 4 to 9 months, three were too early in treatment at the time of the report to assess response. An elderly woman who developed neutropenia, diarrhea, and sepsis died. One patient developed grade 3 neutropenia and another patient developed grade 4 neutropenia. One patient developed grade 3 anemia [49]. We were unable to find any updated reports on this trial.

A trial in non-small-cell lung cancer failed to show a benefit for the addition of celecoxib to chemotherapy. A randomized phase II trial in second-line therapy of non-small-cell lung cancer evaluated the combinations of irinotecan plus docetaxel versus gemcitabine plus irinotecan and either arm with or without celecoxib. They did not find any improvement in median or 1-year survival rates with the addition of celecoxib to either regimen and noted that patients had similar lung cancer symptom scales and toxicity profiles regardless of whether or not they received celecoxib [50].

There is a significant amount of data suggesting that the COX-2 pathway plays a significant role in the pathogenesis of cholangiocarcinoma [27,33,34,51–54]. Whether or not COX-2 inhibitors will be more beneficial as preventive agents or can actually be used for treatment of known cancers remains to be determined. Unfortunately, there have been significant negative reports regarding COX-2 inhibitors in terms of their association with increased risks of myocardial infarction in patients using them [35,55–58]. This negative interaction will make it difficult to pursue prevention trials with these agents. However, in the treatment of incurable cancers, if significant antitumor activity can be shown, the cardiovascular risks may be outweighed by the benefits as has been shown with the use of vascular endothelial growth factor inhibitors. Despite the likely difficulty enrolling patients in COX-2 inhibitor trials, it is important to design further studies to evaluate the role of COX-2 inhibition and treatment outcome. Our case series provides evidence that celecoxib can be safely combined with chemotherapy and that further studies of celecoxib in biliary protocols should be considered.

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