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ORIGINAL ARTICLE

Gemcitabine with carboplatin for advanced biliary tract cancers: a phase II single institution study

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Abstract

Background: Only recently has a standard chemotherapy regimen, gemcitabine plus cisplatin, been established for advanced biliary tract cancers (BTCs) based on a phase III randomized study. The aim of this phase II single-institution trial was to assess the efficacy and safety of gemcitabine combined with carboplatin in the first-line treatment of patients with advanced BTCs.

Methods: Patients with histologically proven BTCs, including cholangiocarcinoma or gallbladder and ampullary carcinomas, were treated with a maximum of nine cycles of intravenous (i.v.) gemcitabine at 1000 mg/m^2 over 30 min on days 1 and 8 with i.v. carboplatin dosed at an area-under-the-curve (AUC) of 5 over 60 min on day 1 of a 21-day cycle.

Results: A total of 48 patients with advanced BTCs (35 cholangiocarcinoma, 12 gallbladder and 1 ampullary cancer) were enrolled. A median of four cycles were administered (range: 1–9). The overall response rate for evaluable patients was 31.1%. Median progression-free survival, overall survival and 6-month survival rates are 7.8 months, 10.6 months and 85.4%, respectively. The most common grade 3–4 toxicities include neutropenia and thrombocytopenia. Grade 3 or 4 non-haematological toxicities were rare.

Conclusions: Gemcitabine combined with carboplatin has activity against advanced BTCs. Our results are comparable to other gemcitabine-platinum or gemcitabine-fluoropyrimidine combinations in advanced BTCs.

Keywords

chemotherapy < cholangiocarcinoma, chemotherapy < gallbladder, cholangiocarcinoma < liver, gallbladder, biliary

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Introduction

Cancers of the biliary tract (BTCs), including intra- and extra-hepatic cholangiocarcinomas and gallbladder cancers, are uncommon cancers accounting for approximately 4% of all gastrointestinal malignancies.[1] An estimated 12 000 new cases of BTCs are diagnosed annually in the United States.[2] Surgical resection remains the only curative treatment for BTCs, however, only a minority of patients diagnosed with these aggressive tumours present at an early, localized and surgically resectable stage. Unfortunately, disease recurrence rates are high despite curative-intent resection of BTCs. Adjuvant chemotherapy, with or without radiation, appears to improve outcomes after resection.[3–5]

As a result of the lack of early symptoms, most patients with BTCs present with locally advanced or metastatic disease. Prognosis is extremely poor for these patients with median

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survival times of less than 1 year.[6–11] A small underpowered randomized study suggests that palliative chemotherapy may offer improvements in quality of life (QOL) and possibly prolong survival for patients with BTCs compared with best supportive care (BSC).[12] Fluoropyrimydine monotherapy provided modest response rates of 0–21% in biliary tract tumours.[13–16] Gemcitabine, as a single agent, and in combination with other antineoplastics, has been extensively studied in patients with BTCs. Single agent gemcitabine conferred response rates of 17% to 36% with median survivals of 6.5–11 months.[17–26] Gemcitabine plus a fluoropyrimidine resulted in response rates of 9.5% to 29%.[27–29] Multiple phase II studies combining gemcitabine with a platinum compound, either cisplatin or oxaliplatin in patients with advanced BTCs, resulted in response rate of 21% to 36% and median survivals of 8.4 months to 15 months.[30–34] Moreover, a pooled analysis of 104 trials with 2810 patients demonstrated a superior response rate, tumour control rate and a trend towards improved time to progression for gemcitabine combined with a platinum compared with fluoropyrimydine-based regimens.[35] Recently, the UK ABC-02 randomized Phase III trial demonstrated superior outcomes for patients treated with gemcitabine plus cisplatin compared with gemcitabine alone. The authors have recommended this regimen to be the new standard regimen for advanced biliary tract cancers.[36]

Compared with cisplatin or oxaliplatin, carboplatin has a better non-haematological toxicity profile and tolerability, less requirement for pre- and post- chemotherapy hydration and minimal risk for nephrotoxicity and cumulative peripheral neuropathy.[37,38] Gemcitabine plus carboplatin has been evaluated in patients with other malignancies and found to be tolerable.[38–40] We now report our phase II study combining gemcitabine with carboplatin for the first-line treatment of patients with advanced BTCs.

Methods

Eligibility

Patients 18 years or older with biopsy-proven advanced, adenocarcinoma of the biliary tract and measurable disease were eligible for this study. Other requirements included the following: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate haematological, renal and hepatic function [absolute neutrophil count (ANC) $\geq$1500/mm^3, platelet count $\geq$100 000/mm^3 and haemoglobin $\geq$9 g/dL, serum creatinine $\leq$2 mg/dL, serum bilirubin $\leq$3.0 mg/dL (biliary stents were allowed), serum transaminases $\leq$ fivefold the institutional upper limits]. Patients must not have received any prior chemotherapy for metastatic disease. Prior adjuvant radiation therapy and chemotherapy was allowed. At least 3 weeks needed to have elapsed since any surgery requiring general anaesthesia. Ineligibility criteria included co-existing severe medical illness and inability to sign consent. The study was approved by the institutional review board and informed consent was obtained from all participants prior to enrolment.

Treatment schedule

Gemcitabine at a dose of 1000 mg/m^2 was administered as a 30-min intravenous (i.v.) infusion on day 1 and 8 of a 21-day cycle. Carboplatin, at an area-under-the-curve (AUC) of 5, was administered as a 1-h i.v. infusion on day 1 of a 21-day cycle. Gemcitabine was administered prior to carboplatin on day 1 of each cycle. Patients received a maximum of nine cycles of therapy. Treatments after the prescribed nine cycles were administered per treating physician discretion. Dose adjustments were made as per a study-defined dose modification table depending on the type and severity of toxicities associated with study treatment.

Assessment of efficacy and toxicity

At study entry, a full history and a physical examination were obtained, including vital signs, height and weight. Prior to enrolment, a complete blood count, comprehensive metabolic profile, β-human chorionic gonadotropin in females, lactic dehydrogenase as well as tumour markers including carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were obtained. Within 28 days of enrolment, baseline tumour measurements were obtained. At the start of each cycle, a history and physical examination were once again performed, as well as a complete blood count, comprehensive metabolic profile and CA19-9 and CEA. Tumour measurements using spiral computed tomography (CT) scans for response were obtained every three cycles (every 9 weeks). Responses were classified according to the Response Evaluation Criteria in Solid Tumors (RECIST).[41] Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

For patients who developed treatment-related toxicities, the doses of gemcitabine and carboplatin were adjusted according to protocol-defined parameters. Treatments were delayed if the ANC was <1500 cells/μl and platelet counts were <100 000 cells/μl or for any Grade III non-haematological toxicities. Upon recovery, gemcitabine doses were reduced by 25% and carboplatin dose was reduced to the calculated AUC dose of four for all subsequent cycles. Two further dose modifications with another 25% reduction in the previous gemcitabine dose and reduction of the carboplatin calculated AUC dose to 3.5 and 3, were allowed. If any further toxicity requiring dose modification occurred after these dose reductions, the patient was removed from the study. The use of granulocyte-colony stimulating growth factors was not allowed, whereas erythropoietin used for anaemia was used at the discretion of the treating physician.

Statistical considerations

The primary objective of this phase II trial was to evaluate the response rate of gemcitabine plus carboplatin in patients with advanced BTCs. Secondary endpoints include tumour control rate, time to progression and overall survival. Descriptive statistical methods were used to summarize baseline patient characteristics and adverse event rates. Progression-free survival and

overall survival rates were calculated using the Kaplan–Meier methodology.

The two-stage design proposed by Simon[42] was used to calculate sample size to reject a response rate of <20% in favour of a response rate of 40%. A sample size of 43 patients was determined to be the number needed to validate the above hypothesis with an alpha error rate of 0.05 and a power of 0.8. Enrolment of a total of 48 patients was planned in the event of a 10% rate of inevaluable or ineligible patients.

Results

Patient characteristics

From March 2002 through to September 2006, 49 patients were enrolled: 35 patients (71%) had cholangiocarcinoma, 12 patients (25%) had gallbladder cancer, 1 patient (2%) had ampullary cancer and 1 patient (2%) was found ineligible after our institutional pathological review of outside slides revealed gallbladder melanoma. The distribution of various baseline patient characteristics is listed in Table 1. The median age at the time of study entry was 63 years (range, 31 to 85).

Table 1 Patient characteristics

Characteristics	*N* (%)
No. of patients enrolled	49
Gender	
Male	15 (31%)
Female	34 (69%)
Performance status	
ECOG = 0	22 (45%)
ECOG = 1 or 2	27 (55%)
Age (years)	
median (range)	63 (31 to 85)
Location of primary tumour (%):	
Cholangiocarcinoma	35 (71%)
Gallbladder	12 (25%)
Ampulla of Vater	1 (2%)
Gallbladder melanoma	1 (2%)
Sites of metastasis (%, *n* = 48)	
Locally advanced	8 (17%)
Metastatic	40 (83%)
Previous surgery	19 (39%)
Curative intent	9 (19%)
Cholecystectomy	2
Right hemihepatectomy	3
Right trisegementectomy	2
Whipple	1
Common bile duct resection	1
Palliative	10 (20%)
Bypass surgery	2
Cholecystectomy	6
Whipple with liver resection	1
Omentectomy	1
Prior radiation	6 (12%)
Prior adjuvant chemotherapy:	5 (10%)
5-FU	3 (6%)
gemcitabine	1 (2%)
gemcitabine-taxotere	1 (2%)
Ca19-9	
At baseline: median/range	64 (2 to 600 435)

Chemotherapeutic drug administration

A total of 227 cycles of chemotherapy were given among the 48 eligible patients. The median number of treatment cycles given to patients was 4 (range 1–9).

Sixteen patients (33%) completed the maximum of nine cycles. Other reasons for discontinuing study treatment include disease progression (29%), toxicity (33%) and consent withdrawal (4%).

During the course of therapy, 36 (75%) out of 48 patients required at least one dose modification secondary to haematological adverse events. Only one-level dose reduction to gemcitabine at 750 mg/m^2 and carboplatin at AUC of 4 was required in 22 patients (46%), whereas 14 patients (29%) required 2 or more dose reductions.

Toxicity

All patients treated on study, including the ineligible patient with melanoma who received one cycle of therapy, were evaluable for toxicity. There was one possible treatment related death in an 80-year-old female patient with cholangiocarcinoma who completed three cycles of chemotherapy on protocol with evidence of stable disease. She subsequently died from non-neutropenic urosepsis and multi-system organ failure.

The grade and distribution of haematological and non-haematological toxicities are summarized in Table 2. The most common haematological toxicities were anaemia (91%), thrombocytopenia (67%) and neutropenia (59%). Grade 3 and grade 4 neutropenia and thrombocytopenia occurred in 37% and 20% of patients, respectively. Four patients developed febrile neutropenia.

The most common non-haematological toxicities observed were fatigue (61%), transaminitis and elevated alkaline phosphatase (41%), nausea (37%), vomiting (28%) and infections without neutropenia (13%). However, grade 3–4 non-haematological toxicities were uncommon. (Table 2).

Eleven patients (22%) required hospitalization, most of which were because of disease progression or reasons unrelated to study therapy. The most common reasons for admission were cholangitis (3), febrile neutropenia (2), sepsis (2), biliary obstruction, suicidal ideation and depression, pain control, dehydration, nausea, ascites, obstructive jaundice, pancreatitis and deep vein thrombosis. Five patients required more than one hospital admission (10%).

Efficacy

Among the 48 eligible patients, 3 were inevaluable for response (discontinuation from study because of an adverse event prior to first radiological assessment). The overall response rate for the 45 eligible patients with BTCs was 31.1% [95% confidence interval (CI), 18.2%-46.7%]. Four patients (8.9%) achieved complete responses and 10 patients (22.2%) had partial responses. Twenty patients (44.4%) had stable disease. Thus, the overall tumour control rate (TCR = CR + PR + SD) was noted to be 75.6% (95% CI, 60.7–87.1%) (Table 3). Eleven patients (24.4%) met the criteria for progressive disease as their best response. A Waterfall plot of the best response detailing the percentage change from baseline tumour measurements for each individual patient is represented in Fig. 1.

Among the 34 evaluable patients with cholangiocarcinoma, 8 patients (23.5%) had a radiological response (1 CR and 7 PR) and TCR of 73.5%. Six out of the 11 patients (54.5%) with gallbladder carcinoma responded to treatment (3 CR and 3 PR) while another 3 patients (27.3%) had SD (TCR = 81.8%).

Tumour marker responses, as defined by a ≥50% decrease of Ca 19-9 from an elevated abnormal baseline value, were observed in 14 out of 45 (31%) patients.

The median progression-free survival (PFS) for all 48 eligible patients was 7.8 months (95% CI, 5.8–9.1 months]. Among the 35 patients with cholangiocarcinoma, median PFS was 7.9 months (95% CI, 5.6–10.5 months] compared with 6.8 months for the 12 patients with gallbladder carcinoma (95% CI, 3.8–9.1 months).

Only one patient remains alive, now 42 months since study entry. Median overall survival for all 48 eligible patients was 10.6 months (95% CI, 8.8–14.2 months) with observed 6-month and 12-month survival rates of 85.4% (95% CI, 71.8–92.8%) and 43.8% (95% CI, 29.6–57.1%), respectively (Fig. 2). Table 3 summarizes the response to therapy and outcomes for all patients and among patients with cholangiocarcinoma and gallbladder cancer. Median survival for patients with gallbladder and cholangiocarcinoma are similar at approximately 11 months. Median overall survival for patients who achieved stable disease was 14.6 months (95% CI, 10.0–23.0 months], comparable to those who achieved a partial or complete response whose median survival was 12.1 months (95% CI, 9.0–19.0 months) (Fig. 3). Patients with progressive disease as their best response had median survival times of only 7.1 months (95% CI, 5.0–9.6 months).

Among the 48 evaluable patients, 19 patients had prior surgery. Curative-intent oncological surgery was performed in

Table 2 Maximum severity, per patient, of grade 3 or 4 adverse events, *n* = 49

Toxicity	Grade 3/ Grade 4	Total
Hematologic		
Anaemia	12%	91%
Thrombocytopaenia	20%	67%
Neutropaenia	37%	59%
Lymphopaenia	18%	59%
Non-haematological		
Fatigue	6%	61%
Transaminitis (AST/ALT) and increase in alkaline phosphatase	4%	41%
Nausea	6%	37%
Vomiting	6%	28%
Infection without neutropaenia	4%	13%
Hyperbilirubinaemia	2%	10%
Diarrhoea	4%	8%
Febrile neutropaenia with infection	6%	6%
Febrile neutropaenia without infection	2%	2%

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3 Response rates, progression-free survival and overall survival for all patients, and by disease site

	Total patients	Cholangiocarcinoma	Gallbladder cancer
Response			
N	45[a]	33	11
Response rate, %	31.1% (95% CI, 18.2–46.7%)	23.5%	54.5%
Stable disease, %	44.4%	50%	27.3%
Tumour-control rate, %	75.6% (95% CI, 60.5–87.1%)	73.5%	81.8%
Survival (ITT)			
n, eligible patients	48[b]	35	12
Progression-free survival, months	7.8 (95% CI, 5.8, 9.1)	7.9	6.8
Overall survival, months	10.6 range = 1–45 (95% CI, 9–15)	10.6 Range = 3–42	11.5 Range = 1–45
6-month survival, %	85.4% (95% CI, 71.8–92.8%)	83.3%	91.7%
12-month survival, %	43.8% (95% CI, 29.6–57.1%)	42.4%	50.0%

[a]All evaluable patients including one patient with ampullary cancer.
[b]All eligible patients, including one patient with ampullary cancer.

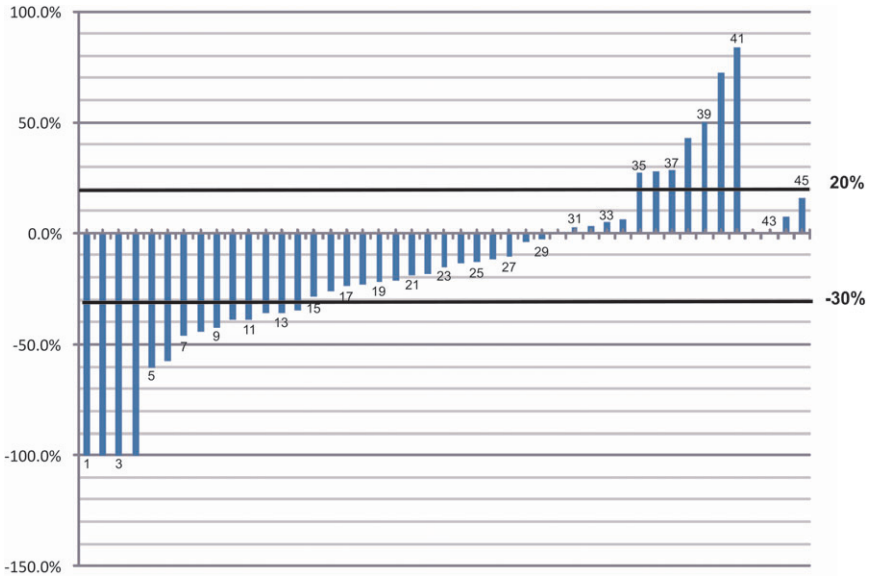

Figure 1 Waterfall Plot. Best objective tumour response for each patient: maximum change in the sum of the longest diameter of measurable disease from baseline. *n* = 45 complete/partial responders: >30% decrease; stable disease: <30% decrease to <20% increase; progressive disease: >20% increase or with new lesions

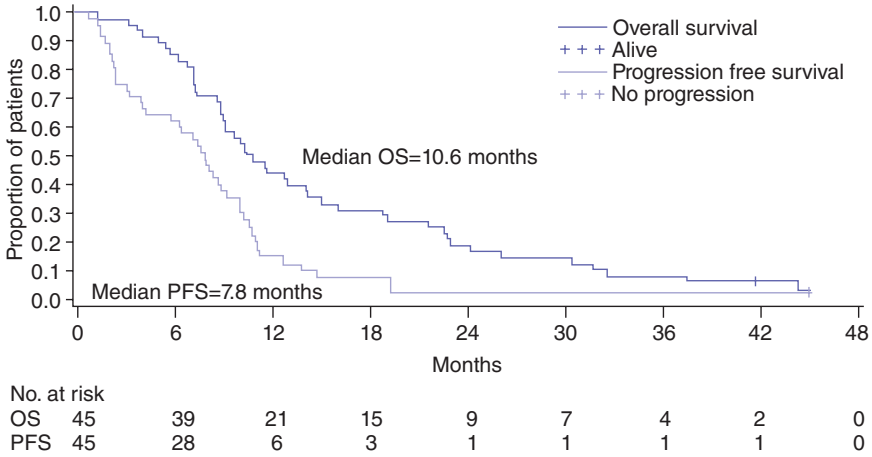

Figure 2 Overall and progression-free survival. *n* = 45

nine patients who later experienced disease recurrence. Surgery for 10 patients was palliative in intent, as metastatic disease was noted during surgery. Median survival for the 19 patients with prior surgery, whether curative or palliative, was 10.1 months, slightly worse than those who had no prior surgery (12.1 months).

Discussion

Although biliary tract cancers are relatively uncommon, it is a devastating disease, usually presenting at advanced stages when surgery is not a treatment option. Few therapeutic advances have been made in the recent era with regard to new drug development for unresectable, locally advanced or metastatic biliary tract cancers. Multiple agents have been investigated as single or combination therapies in small uncontrolled studies. Historically, 5-fluorouracil (5-FU) has been the most studied agent and has the longest track record in treating patients with advanced biliary tract cancers. 5-FU, as single agent therapy, has a response rate of 0–21%.[13–16] Other agents, such as mitomycin-C,[43] methotrexate,[44] etoposide,[45] docetaxel,[46] and doxorubicin,[47] have been used with mixed results in biliary tract cancers. Only 10–20% of patients treated with the above chemotherapies showed a response.

Gemcitabine has been evaluated both as a single-agent and in combination with numerous agents. Most of these studies were limited as a result of small sample sizes (Table 4). A recent pooled analysis of 104 clinical trials evaluating gemcitabine plus a plati-

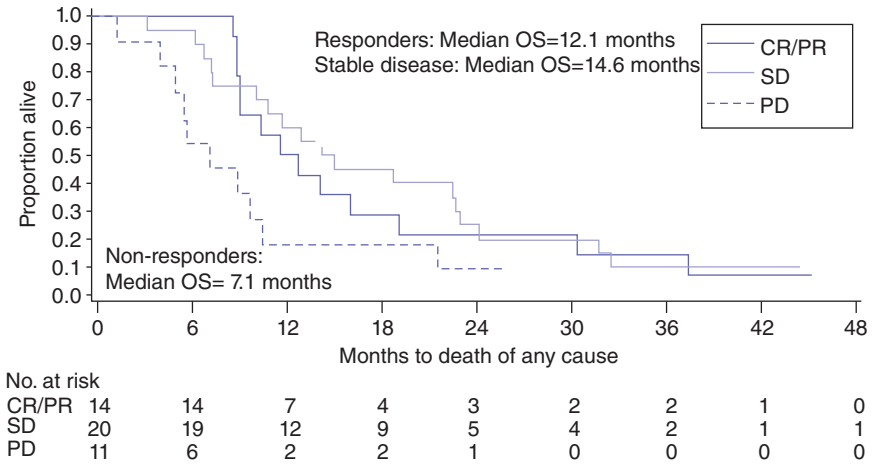

Figure 3 Overall survival based on response. $n = 45$

num regimen in biliary tract cancer[35] reported that the pooled RR and TCR was 22.6% and 57.3%, respectively. Significant correlations of RR and TCR with survival times were found.[35]

Recently, gemcitabine in combination with cisplatin has been evaluated in 410 patients with advanced or metastatic cholangiocarcinoma, gallbladder cancer and ampullary cancers in a large, randomized phase III clinical trial.[36] Gemcitabine plus cisplatin conferred a significantly superior median overall survival (OS) compared with those treated with single-agent gemcitabine [11.7 months vs. 8.2 months, $P = 0.002$, hazard ratio (HR) = 0.68, 95% CI 0.53–0.86]. The median PFS was also significantly greater with gemcitabine/cisplatin than gemcitabine alone (8.5 vs. 6.5 months, $P = 0.003$, HR = 0.70, 95% CI, 0.56–0.88). Although the response rate for the combination arm was higher (25.7% vs. 16%), this was not statistically significant compared with gemcitabine alone. Toxicities were similar in both arms, however, neutropenia was found to be more common in the combination arm. This large phase III study established a new standard first-line regimen using gemcitabine with cisplatin for advanced biliary cancer.

In this single institution phase II clinical trial we demonstrate that gemcitabine with carboplatin has activity in biliary tract cancer with an overall response rate of 31.1%, tumour control rate of 75.5%, median time to progression of 7.8 months and median overall survival of 10.6 months. The 6-month and 1-year survival rates were 85.4% and 43.8%, respectively. These results are comparable to those reported by Valle *et al.* in their randomized study using gemcitabine and cisplatin in a similar population of patients with biliary tract tumours.[36] These results are also consistent with other phase II studies using gemcitabine-based combinations and the pooled analysis data published by Eckel[35] (Table 4).

As there appears to be differences in the clinicopathological behaviour of the different tumour types comprising these rare biliary tract malignancies, a subset analysis of outcomes for patients with cholangiocarcinomas and gallbladder cancers was done. Although the clinical response rate appears to be higher among patients with gallbladder cancer, compared with patients with cholangiocarcinoma, OS for both groups are identical at approximately 11 months. Patients with stable disease as their best response still achieved comparable survival times similar to those who achieved partial or complete responses. Similar to the clinical experience in pancreatic cancer, significant benefits in outcome can be observed despite low response rates to chemotherapy. Unfortunately, most patients progress and die of their malignancy, including the four patients who achieved a complete radiological response to treatment. Patients with prior surgery, whether curative or palliative, appear to have a shorter median survival time compared with those who never had any prior surgery. However, this observation needs to be validated in larger studies.

Although severe non-hematological toxicities were uncommon, haematological toxicities associated with gemcitabine and carboplatin, as administered in this protocol, appear higher compared with the toxicities reported using weekly cisplatin and gemcitabine in the ABC-02 study (Grade 3–4 anemia 12% vs. 6.3%; grade 3–4 thrombocytopenia 20% vs. 8.2% and grade 3–4 neutropenia 37% vs. 22.6%).[36] Haematological toxicities associated with this regimen were also higher than other combinations such as gemcitabine with capecitabine.[29]

Gemcitabine in combination with carboplatin has activity against advanced biliary tract cancers comparable to other gemcitabine-platinum and gemcitabine fluoropyrimidine combinations. However, haematological toxicities associated with this combination are significant. This combination should be evaluated among patients who may be intolerant or not suitable for cisplatin. Further large multicentre randomized trials, preferably with pharmacogenomic and tissue correlative studies, are necessary to establish more efficacious and tolerable regimens to treat patients with these rare malignancies.

Table 4 Selected published studies of various regimens for biliary tract cancer

Author, year [reference]	Regimen	Dose and Schedule	N	Response Rate	TCR	Median PFS, months	Median OS, months
Choi *et al*., 2000[16]	Leucovorin 5-FU	25 mg/m^2/day 1–5, 375 mg/m^2/day 1–5, q28d	28	32.1%	–	–	6
Arroyo *et al*., 2001[25]	Gemcitabine	1000 mg/m^2 on D1, 8, 15 q28 days	42	36%	64%	3.9	6.5
Alberts *et al*., 2005[27]	Gemcitabine 5-FU Leucovorin	1000 mg/m^2 on D1, 8,15 600 mg/m^2 IVP on D1 25 mg/m^2 on D1, q28d	42	9.5%	23%	4.6	9.7
Riechelmann *et al*., 2007[28]	Gemcitabine Capecitabine	1000 mg/m^2 on D1, 8 650 mg/m^2 PO BID x14d, q21d	75	29%	78%	6.2	12.7
Koeberle *et al*. 2008[29]	Gemcitabine Capecitabine	1000 mg/m^2 on D1,8 650 mg/m^2 PO BID, D1-14	44	25%	80%	7.2	13.2
Kim *et al*., 2006[32]	Gemcitabine Cisplatin	12 500 mg/m^2 on D1, 8 60 mg/m^2 on D1, q21d	29	34.5%	48.3%	3.0	11
Harder *et al*., 2006[33]	Gemcitabine Oxaliplatin	1000 mg/m^2 on D1, 8,15 100 mg/m^2 on D1, 8 q28d	31	26%	71%	6.5	11
Kim *et al*., 2009[26]	Gemcitabine Oxaliplatin	1000 mg/m^2 on D1, 15 85 mg/m^2 on D2, 16 q28d	40	15%	52.5%	4.2	8.5
Eckel *et al*., 2007[34]	Gemcitabine platinum	Various	2810	22.6%	57.3%	4.1	8.2
Valle *et al*., 2009[35]	Gemcitabine Gemcitabine Cisplatin	1000 mg/m^2 on D1,8,15 q 28d 1000 mg/m^2 on D1,8 25 mg/m^2 on D1,8 q21d	206 204	16% 25.7%	71.2% 79.1%	6.5 8.4	8.3 11.7
Williams-Current study	Gemcitabine Carboplatin	1000 mg/m^2 D1,8 AUC 5 D1, q 21d	48	31.1%	75.6%	7.8	10.6

5-FU, 5-fluoropyrimidine; PFS, progression-free survival; N, number of patients; OS, overall survival; TCR, tumour control rate.

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Conflicts of interest

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