symposium article

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Gemcitabine and oxaliplatin combination chemotherapy in advanced biliary tract cancers

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Background: Biliary tract cancers are uncommon tumors with a poor prognosis and most patients present with invasive and inoperable disease at diagnosis. Chemotherapy represents a palliative treatment, with poor response rates and a median survival of less than 6 months. Oxaliplatin and gemcitabine have shown an interesting activity as single agents in this group of patients.

Patients and methods: We carried out a multicenter phase II study to evaluate the efficacy and safety of combined oxaliplatin and gemcitabine in locally advanced and metastatic biliary tract carcinoma. The schedule of chemotherapy included oxaliplatin 100 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8, every 21 days.

Results: All the 24 patients were evaluable for response and toxicity. According to RECIST criteria we observed one complete response and 11 partial responses for an overall response rate of 50%. Overall survival for all the patients on study was 12 months (range 2–30). According to WHO criteria, three patients (12.5%) suffered grade 3 neutropenia and three patients (12.5%) grade 3 thrombocytopenia. Only two patients (8%) suffered grade 3 neuropathy.

Conclusions: Oxaliplatin and gemcitabine chemotherapy seems to be effective with a favorable safety profile in first-line chemotherapy of advanced biliary tract cancers.

Key words: advanced biliary tract cancer, oxaliplatin, combination therapy

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introduction

Biliary tract cancers are uncommon tumors with a poor prognosis and most patients present with invasive and inoperable disease at diagnosis [1]. Chemotherapy represents a palliative treatment, but single or combination-drug schedules have demonstrated poor response rates with a median survival of less than 6 months [2]. Fluoropyrimidines have been considered the basis of palliative chemotherapy despite response rates in the range of 0%–10%. Older combination chemotherapy, including fluorouracil (FU), has not demonstrated a clear superiority over single-agent FU but have resulted in added toxicity [3, 4]. A number of recent phase II trials using newer chemotherapeutic agents suggest a level of chemosensitivity not previously seen. Gemcitabine, newer FU regimens, capecitabine and platinum analogs all seem to be active and, perhaps, are more active in combinations [5]. The larger phase II trials report objective response rates (ORRs) ranging from 15% to 45% [6]. Differences in response rates between gall-bladder and cholangiocarcinoma have not been seen; however, some series report poorer overall survival for patients with gall-bladder cancer compared with cholangiocarcinoma [7].

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The nucleoside analog gemcitabine is a chemotherapeutic agent with a favorable therapeutic profile. It has shown ORRs ranging from 15% to 35% in a number of phase II trials in biliary cancers and seems consistently active and well tolerated as a single agent [8–11]. Among the newest drugs, significant anti-tumor activity, at a very low level of toxicity in the treatment of gastric and colon cancer has been more recently shown for the novel diaminocyclohexane (DACH) carrier ligand-based/platinum compound, oxaliplatin (OX), alone or in combination with 5-FU and FA (FUFA) [12]. Preliminary results of phase I and II trials of gemcitabine in association with oxaliplatin in patients with advanced biliary tract carcinoma have shown a good toxicity/efficacy ratio for the combination [13–16]. On the basis of these data we carried out a phase II study of combination therapy with oxaliplatin 100 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8 every 3 weeks in patients with advanced biliary tract carcinoma.

patients and methods

Patients were eligible if they had pathologically proven, measurable, unresectable, locally advanced or metastatic adenocarcinoma arising from the intra- and extrahepatic biliary ducts or gall-bladder. No prior chemotherapy for advanced disease was allowed. Additional inclusion criteria included age 18 years, Eastern Cooperative Oncology Group (ECOG) [17] performance status ≤2, and adequate organ functions [neutrophils 1.5 × 10/l, platelets 100 × 10/l, serum creatinine 160 μmol/l or

actual or calculated creatinine clearance 60 ml/min, ALT 5 × upper limit of normal (ULN), and total bilirubin 3 × ULN and stable for 2 weeks]. Written informed consent was obtained from each patient. The protocol and the informed consent form were approved by the local ethical committee.

treatment plan

Patients were treated on a 3-week cycle, with dosing based on the recommended dose from phase I and II studies in literature [18–20]. Gemcitabine was administered intravenously over 30 min on days 1 and 8 of each cycle at a fixed dose of 1000 mg/m^2. Oxaliplatin was administered intravenously over 3 h on day 1 at 100 mg/m^2 after gemcitabine infusion. Treatment was continued until progression, unacceptable toxicity, or withdrawal of patient consent. Adverse events were recorded according to the National Cancer Institute Common Toxicity Criteria [21]. Dose adjustments and delays were allowed for each drug. Gemcitabine and oxaliplatin doses were reduced by 25% on all subsequent cycles for febrile neutropenia, grade 4 hematologic toxicity lasting for more than 7 days, or bleeding-associated thrombocytopenia. Chemotherapy doses were reduced by 25% on day 8 for an absolute neutrophil count of 500–1000/μl or a platelet count of 50 000 to 100 000/μl. For patients on progression and with good performance status, a 5-FU based single-agent chemotherapy was planned as second-line chemotherapy.

assessment

Tumor response was assessed using Response Evaluation Criteria in Solid Tumors [22] with computer tomography scans at baseline and every three cycles of treatment. Responses were confirmed by computed tomography at least 4 weeks later. The primary investigation of interest was the tumor ORR, with secondary investigations including overall and progression-free survival, safety and tolerability of this treatment. Summary statistics, such as the median and range, were used to describe the patient sample. The Kaplan–Meier method [23] was used to estimate overall and progression-free survival outcomes. Survival curves were compared with the log-rank test. All tests were two-sided, and a $P < 0.05$ was considered statistically significant.

results

Twenty-four patients (15 males and nine females) with advanced biliary cancer were enrolled between October 2002 and January 2004. Nine patients had carcinoma of the gall-bladder and 15 had cholangiocarcinoma or extrahepatic biliary system disease. Demographics and other baseline characteristics are listed in Table 1. Thirteen patients had a PS = 0, seven patients had a PS = 1 and four patients had a PS = 2. Ten patients had metastatic disease, six of which experienced disease recurrence after a prior resection with curative intent. Eight patients had undergone exploratory laparotomy to determine unresectability, whereas the remaining 16 were clearly unresectable based on radiological evidence of distant metastatic disease. Most patients had a good performance status at the start of therapy (ECOG performance status of 0–1 in 20 patients) and the median age was 68 years (range 59–73 years). All patients were assessable for efficacy and toxicity analysis. Over 120 cycles of Gem Ox chemotherapy were delivered, with a median of four cycles per patient (range one to eight cycles). Across all cycles, patients received more than 90% of initial prescribed chemotherapy. The primary reason for discontinuing treatment was progressive disease (20/24 patients who completed treatment). Two patients requested a break and two discontinuations were at the physician's discretion because of other comorbidities. Median follow-up time per patient was 13 months (range 1.1–30 months). According to RECIST criteria we observed one complete response (CR) and 11 partial responses (PR) for an overall response rate of 50%. Five stable disease (SD) and seven progressive disease (PD) also occurred. Table 2 shows the responses divided for gall-bladder cancer and cholangiocarcinoma. The responders (PR + CR) demonstrated a TTP of 10 months (range 6–24) and an overall survival of 18 months (range 6–30), while the overall survival for all the patients in the study was 12 months (range 2–30). Figures 1 and 2 demonstrate the progression-free survival and overall survival curves for patients with gall-bladder or bile ducts cancers: there was no statistically significant difference. Of note, 11/24 patients received a second-line 5-FU based chemotherapy after progression of disease. Two patients with locally advanced disease with objective response underwent surgical procedure.

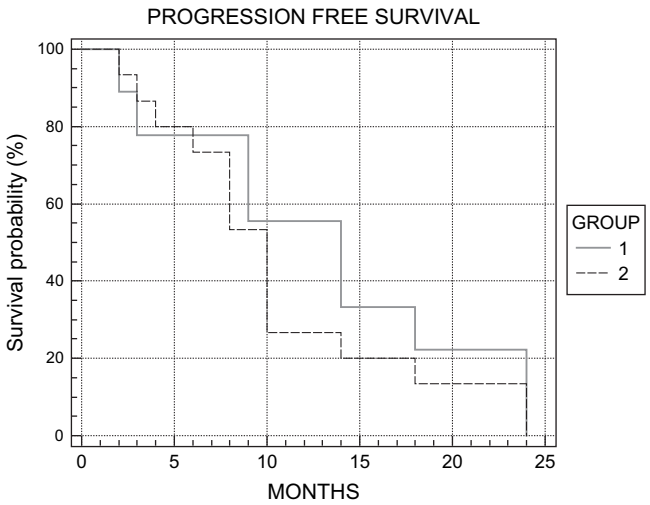

Figure 1. Progression-free survival for patients with gall-bladder cancer (Group 1) and bile ducts cancers (group 2).

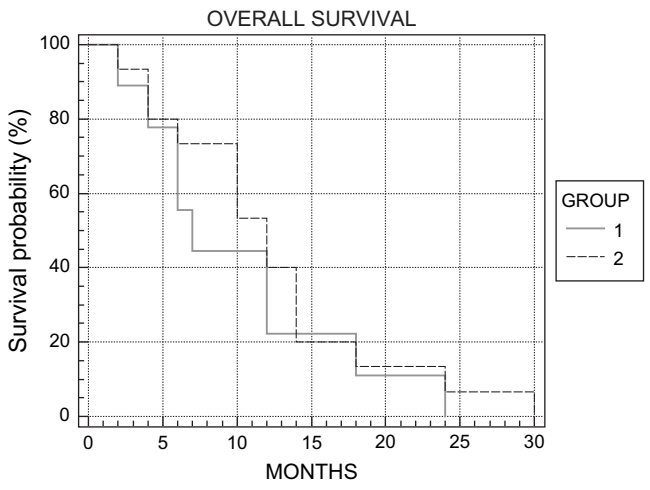

Figure 2. Overall survival for patients with gall-bladder cancer (Group 1) and bile ducts cancers (group 2).

Table 1. Patient characteristics

Characteristic	No. of patients (n = 24)
Disease	
Metastatic	10
Locally advanced	14
Bile ducts	15
Gall-bladder	9
Sex	
Female	14
Male	10
Age, years	
Median	62
Range	38–75
ECOG performance status at baseline	
0	13
1	7
2	4
Biliary stent or bypass	8
Prior therapy	
Primary resection	12
Adjuvant chemoradiation	0

ECOG, Eastern Cooperative Oncology Group.

Table 2. Best overall tumor response

Tumor type	CR		PR		SD		PD		ORR + SD Disease Control	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total, all types (n = 24)	1	4	11	45	5	20	7	29	17	70
Bile ducts cancers (n = 15)	1	6	7	46	3	20	4	26	11	73
Gall-bladder cancer (n = 9)	0	0	4	44	2	22	2	22	6	66

CR, complete response; PR, partial response; SD, stable disease for minimum of three cycles; PD, progressive disease; ORR, objective response rate.

Table 3. Toxicity in any cycle

Toxicity	Grade 1–2		Grade 3		Grade 4	
	No. of patients	%	No. of patients	%	No. of patients	%
Neutropenia	7	29	3	12	0	0
Anemia	0	0	0	0	0	0
Thrombocytopenia	3	12	3	12	0	0
Sensory neurophaty	8	33	2	8	0	0
Fatigue	11	45	5	20	0	0
Nausea/vomiting	6	25	1	4	0	0
Mucositis	3	12	0	0	0	0
Diarrhea	2	8	0	0	0	0

Table 3 reports the most important toxicities. According to WHO criteria, three patients (12.5%) suffered grade 3 neutropenia and three patients (12.5%) grade 3 thrombocytopenia. One-third of patients developed grade 1–2 peripheral neuropathy and only two patients (8%) suffered grade 3 neuropathy. Grade 1–2 nausea/vomiting was present in six patients (25%) and only one patient (4%) suffered grade 3 nausea/vomiting. Grade 3 fatigue was observed in five patients (20%) and mild fatigue during treatment (grade 1–2) was reported in 45% of patients. There was no difference in toxicity between patients with gall-bladder cancers and patients with bile duct cancers. No treatment-related liver toxicity was observed in any of the patients on this study. This combination of GemOx was generally well tolerated. There were no treatment-related deaths. No patients discontinued treatment because of toxicity.

discussion

No effective standard therapy is yet available for advanced biliary tract cancer. Only relatively small phase II trials have assessed the efficacy and toxicity profiles of chemotherapy regimens in the palliative treatment of gall-bladder cancer and cholangiocarcinoma. Due to tumor-specific complications, such as obstructive jaundice with impaired hepatic metabolism and biliary excretion, toxicity profiles of chemotherapy regimens may be different in gall-bladder and biliary tract carcinoma compared with other cancers. Single-agent and multiagent regimens have yielded modest results in patients with advanced biliary carcinomas. Overall response rates and disease control rates are about 25% (mostly 13%–35%, range 0%–64%). With regard to combination therapy, Table 4 summarizes the most recent trials in advanced biliary tract cancer [11, 12, 24–33].

Preclinical results of previous studies have demonstrated that the difluorinated analogue of deoxy-cytidine difluoro-2′,2′-deoxycytidine gemcitabine (GEM), synergistically interacts with oxaliplatin in terms of anti-tumor activity *in vitro* [15, 16]. Moreover Mouvradis et al. [20] demonstrated the feasibility and safety of gemcitabine–oxaliplatin (GEM–OX) combination chemotherapy in a phase I study involving patients with advanced solid tumors: the maximum tolerated dose was not reached, the combination was well tolerated with a manageable toxicity of doses up to 1400 mg/m^2 of gemcitabine on days 1 and 8 and doses up to 120 mg/m^2 of oxaliplatin.

Based on the important data on pancreatic cancer, Andre et al. verified the activity and tolerability gemcitabine–oxaliplatin (GEM–OX) combination in 33 patients with advanced biliary tract adenocarcinoma. All received gemcitabine 1000 mg/m^2 as a 10 mg/m^2/min infusion on day 1, followed by oxaliplatin 100 mg/m^2 as a 2-h infusion on day 2, every 2 weeks. Tumor sites were gall-bladder (9 patients), extrahepatic bile ducts (5 patients), ampulla of vater (3 patients) and intrahepatic bile ducts (7 patients). National Cancer Institute Common Toxicity Criteria grade 3–4 toxicities were neutropenia 14% of patients, thrombocytopenia 9%, nausea/vomiting 5% and peripheral neuropathy 7% [14].

Our experience is slightly different from this: the schedule of treatment was different with gemcitabine administered on days 1 and 8 and oxaliplatin on day 1 after gemcitabine every 3 weeks. The lower toxicity observed in our study is probably due to this different schedule of treatment. Median survival achieved by our patients was 12 months and therefore in the range of most other

Table 4. Most recent combination therapy trials in biliary tract cancers

Study	Regimen	Total	BD	GB	RR (%)	Toxicity[a]	Median survival (months)
Gebbia V et al. [24]	Gemcitabine	18	6	12	22	+	8
	Gemcitabine–5-FU FA	22	NR	NR	36	++	11
Taieb et al. [25]	Cisplatin–5-FU	29	19	10	34	+	9.5
Hsu et al. [26]	Gemcitabine –5-FU FA	30	25	5	20	+++	4.7
Kuhn et al. [27]	Gemcitabine–docetaxel	43	NR	NR	9	+++	11
Reyes-Vidal et al. [11]	Gemcitabine–cisplatin	44	0	44	45	++	7
Dorval et al. [12]	Gemcitabine–cisplatin	30	0	30	36	+++	5
Rao et al. [28]	Epirubicin–cisplatin–FU	23			19	++	9.2
	FU–etoposide–FA	24			16	+++	12
Nehls et al. [13]	Capecitabine–oxaliplatin	29	19	10	21	++	9.5
Kornek et al. [29]	MMC–gemcitabine	25	18	7	20	+/++	6.7
	MMC–capecitabine	26	19	7	31	+/++	9.3
Andrè et al. [14]	Gemcitabine–oxaliplatin	33	20	13	33	+/++	15.4
Cho et al. [30]	Gemcitabine–capecitabine	44	37	7	32	+/++	14
Knox et al. [31]	Gemcitabine–5-FU	27			33	+	5.3
Knox et al. [32]	Gemcitabine–capecitabine	45	24	21	31	+	14
Kim et al. [33]	Gemcitabine–cisplatin	29	29	0	34.5	+++	11
Current study	Gemcitabine–oxaliplatin	24	15	9	50	+	12

BD, bile duct cancer; GB, gall-bladder cancer; RR, response rate; MMC, mitomycin; FA, folinic acid; FU, fluorouracil; NR, not reported.
[a]Toxicity: reported >grade 3 non-hematologic or significant hematologic toxicity: +, mild, <20%; ++, moderate, 20%–40%; +++, severe, >40%.

studies investigating combination chemotherapy for biliary tract cancer. Progression-free survival was similar to other published data of phase II trials in biliary tract cancer (Table 4). We observed no difference in survival and toxicity in patients with gall-bladder and bile ducts cancers.

The prolongation of overall survival may be influenced by the possibility of administering a 5-FU based second-line chemotherapy Another important fact to outline is the impressive rate of control disease in both groups of patients and the possibility of surgery in two responding patients with locally advanced disease. It would be interesting to have more data about a comparison between single-agent chemotherapy versus combination therapy in terms of benefit on quality of life and survival. However, such randomized studies are very difficult to carry out for the elevated number of patients requested and for the difficulties in the patients' selection.

In conclusion, combination chemotherapy with gemcitabine and oxaliplatin seems to be a very promising regimen with tolerable toxicity in advanced biliary tract cancers. Further randomized studies comparing gemcitabine monotherapy with gemcitabine oxaliplatin combination therapy are warranted to identify the standard of treatment.

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