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ORIGINAL ARTICLE

Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder cancer: a Korean Cancer Study Group phase II trial

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Abstract
Purpose Chemotherapy represents a palliative treatment, with poor response rates and a median survival of less than 6 months in patients with biliary tract cancers (BTCs). The aim of this study was to evaluate the efficacy and safety of the combination chemotherapy with gemcitabine and oxaliplatin (GEMOX) in patients with BTCs including gall bladder cancer.
Methods We carried out a nationwide multicenter phase II study evaluated the efficacy and safety of GEMOX as first-line therapy in patients with advanced BTCs. Eligible patients with previously untreated locally advanced or

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metastatic BTCs received gemcitabine 1,000 mg/m^2 (day 1 and 8) and oxaliplatin 100 mg/m^2 (day 1), every 3 weeks.
Results Fifty-three patients were evaluated, 60% had cholangiocarcinoma and the remaining 40% gall bladder cancer; the objective response rate was 18.9% (10/53 patients including 1 Complete response) [14.9%; 95% confidence interval (CI), 7.4–25.7%] in the treated population. Stable disease were observed in 27/53 (50.9%) patients, disease control rate was achieved in 69.8% of all patients. Median progression-free survival was 4.8 months (3.1–6.5, 95% CI) and median overall survival was 8.3 months (5.8–10.8, 95% CI). Grade 3/4 toxicities included neutropenia (33.9% of patients) and thrombocytopenia (7.6%).
Conclusions The GEMOX regimen demonstrated a modest antitumor activity and is well tolerated in patients with advanced BTCs.

Keywords Biliary tract cancers · Chemotherapy · Gemcitabine · Oxaliplatin

Introduction

Biliary tract cancers (BTCs) are invasive cancers that arise from the epithelial lining of the gall bladder and bile ducts comprising intrahepatic, perihilar and extrahepatic biliary tree. Worldwide, BTCs account 3% of all gastrointestinal cancers with geographic variation and the reported incidence is the highest in Southeast Asia, Israel and Japan [9, 14]. In South Korea, incidence of BTCs is common, and annually, approximately 3,500 new patients are diagnosed, and BTCs account for 6% of all cancer deaths [16]. In western areas, cholangiocarcinoma was relatively uncommon but intrahepatic cholangiocarcinoma has been rising over past two decades in the United States [14] (see Figs. 1, 2).

Although surgical resection is the mainstay of curative treatment modality, less than 25% of patients are candidates for curative resection [4, 13]. Even in patients with resectable tumors undergoing aggressive surgery, the general outcome is disappointing and their median overall survival is less than 1 year [1]. For patients with advanced biliary tract cancer (ABTC) who are away from curative intent, best supportive care or chemotherapy is recommended as a palliative treatment option. A benefit over best supportive care has been demonstrated for palliative chemotherapy to diminish symptoms and possibly to extend survival [7]. However, due to the lack of randomized phase III trial data, no definite standard chemotherapy has been established in the palliative treatment of ABTC.

To date, based on published results of predominantly phase II trials, gemcitabine, a deoxycytidine analog related to cytarabine has been shown to be an active single agent therapy in BTC [10, 15]. Although response rates vary widely when used as a single agent, there is evidence to suggest that gemcitabine may produce a clinical benefit response in a substantial subset of patients [10, 15]. Accumulating data from recent phase II trials show that gemcitabine combined with platinum drugs including cisplatin represents an active and tolerated treatment option in the treatment of BTC [5, 11, 17]. Recently oxaliplatin can replace the classic cisplatin to reduce the emetic and potential renal toxicity without compromising efficacy [3]. Some single center studies on BTC with gemcitabine/oxaliplatin combination have reported variable results and suggested clinical benefits to be confirmed [8, 12]. Here, we conducted a nationwide multicenter study to evaluate the efficacy and safety of the combination chemotherapy with gemcitabine and oxaliplatin (GEMOX) in patients with ABTCs including gall bladder cancer (GBC).

Patients and methods

Eligibility criteria

Patients aged >18 years with histologically or cytologically confirmed and locally advanced or metastatic adenocarcinoma in the biliary tract (intrahepatic or extrahepatic bile ducts) or gallbladder were enrolled. Other enrolling criteria were as follows: one or more unidimensionally measurable lesions on computed tomography (CT) or magnetic resonance imaging (MRI); Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2: adequate hematologic (neutrophil $\geq$ 1,500/μl, platelets $\geq$ 100,000/μl), renal [serum creatinine $\leq$ 1.5 $\times$ upper normal value (UNL)] and hepatic (alanine aminotransferase $\leq$ 3 $\times$ UNL (incase of liver metastasis, $\leq$5 $\times$ UNL), bilirubin $\leq$ 3 mg/dl) function; Life expectancy over 3 months. Patients with obstructive jaundice in whom the biliary tree could be decompressed by internal stent, with a subsequent reduction in bilirubin level to $\leq$3 mg/dl, were allowed to be enrolled. All patients provided written informed consent.

Patients were excluded in case of preexisting malignancy, cerebral metastases or severe comorbidities. Patients were not allowed to have received any type of prior chemotherapy. Radiotherapy covering target lesion was not permitted. Women were either postmenopausal or using

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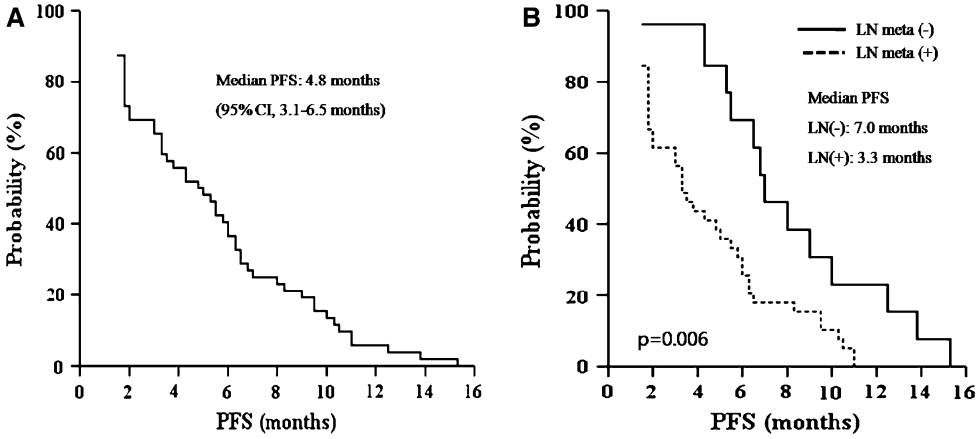

Fig. 1 Progression-free survival **a** for total study population and **b** subgroup analysis of patients according to LN metastasis

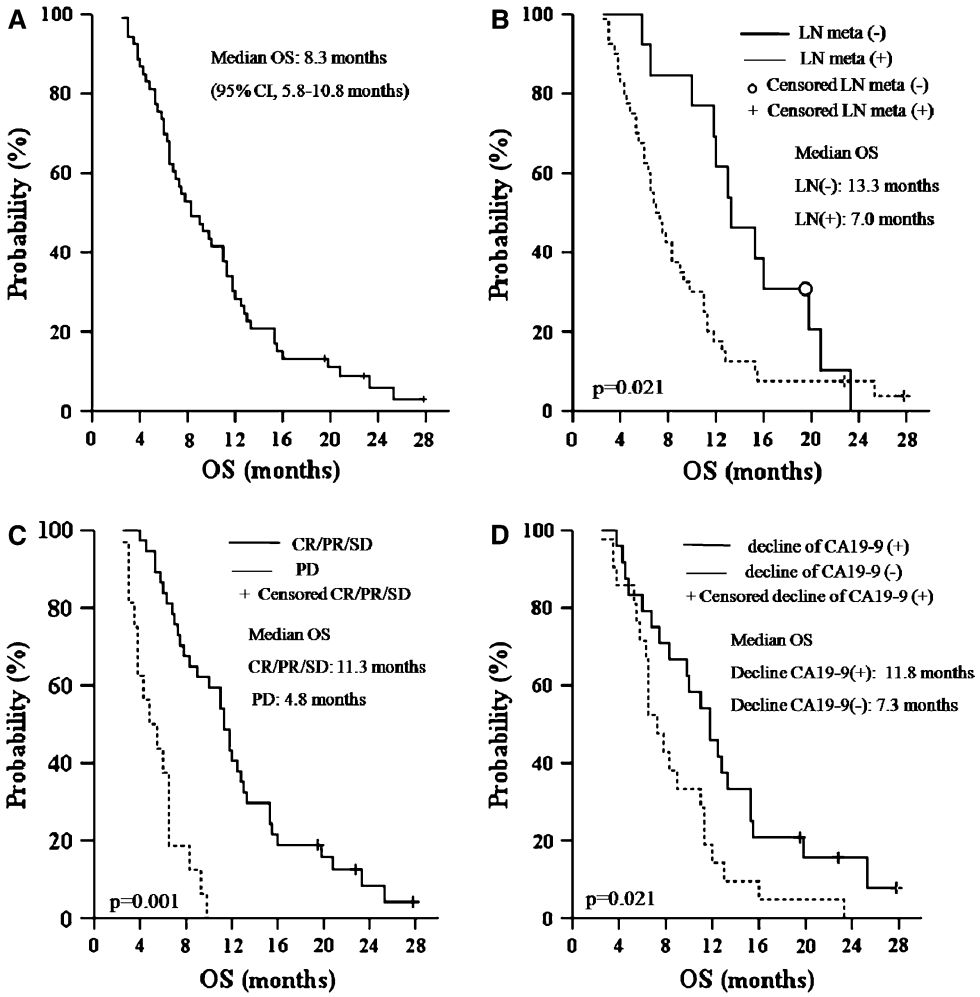

Fig. 2 Overall survival **a** for total study population, **b** subgroup analysis of patients and according to LN metastasis, **c** Clinical benefit, and **d** achievement of ≥10% decline of CA19-9

adequate contraception with whom childbearing potential. The study was approved by the local ethics committees.

Treatment schedule

All patients received the treatment protocol as follows: gemcitabine 1,000 mg/m^2 IV infusion for 1 h on days 1, 8, and oxaliplatin 100 mg/m^2 more than 2 h on day 1. Treatment was repeated every 3 weeks. National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0 was used for toxicity assessment. Treatment was continued until disease progression, unacceptable toxicity despite dose modification, treatment delay more than 3 weeks or patient's withdrawal of consent. In case of cumulative sensory peripheral neuropathy NCI-CTC-adverse event grade 2 persisting over 7 days, the dose of oxaliplatin was

reduced to 75 mg/dl. Oxaliplatin was stopped in case of grade 3 or 4 peripheral sensory neuropathy and reintroduced after recovery to grade 2 or less.

For patients with neutrophil <1,500/μl, platelets <100,000/μl, treatment was delayed for 7 days up to 3 weeks. If recovery occurred within the 7 days, treatment was continued without dose reduction; otherwise, the dosages of gemcitabine and oxaliplatin were reduced to 75% doses. Gemcitabine dose was reduced by 25% on day 8 for an absolute neutrophil count of 500–1,000/μl or a platelet count of 50,000–100,000/μl. For grade 3/4 neutropenia, thrombocytopenia, mucositis, or asthenia, the doses of gemcitabine and oxaliplatin were reduced to 75% doses on all subsequent cycles. If grade 3/4 toxicities developed after dose reduction, the patient could be considered to be off the study.

Treatment evaluation and statistics

Tumor response was assessed after every two cycles of treatment using Response Evaluation Criteria in Solid tumors (RECIST) with computed tomography (CT) or magnetic resonance imaging (MRI) scan. Objective responses were to be confirmed at least 1 month later. Primary end point of the study was to evaluate response rate. Secondary end points included overall survival (OS), progression-free survival (PFS) and toxicity profile. PFS was determined from the first day of treatment until tumor progression assessed by CT scan or MRI. OS was determined from the first day of treatment to the date of death. Kaplan–Meier methodology was used to describe the distribution of survival.

Considering the results of previous trials using gemcitabine-based regimens for ABTC as overall response rate of 15–20%, we expected 15% potential benefit in response rate. So the study was designed following assumptions: H0: Response rate (RR) $\leq$ 20% and H1: RR $\geq$ 35%, a significance level of 0.05 and a power of 80%. At least a sample of 50 patients was required. Assuming that 10% of patients would be inassessable, a total of 55 patients was planned to be accrued for the study. The relative dose intensity (RDI) was calculated as the ratio of the actual DI to the planned DI in the protocol (actual DI = total dose given during the study/duration in weeks).

Results

Patients characteristics

From November 2006 through November 2008, 55 patients were recruited and 53 patients were evaluated in 13 centers in South Korea. Two patients did not complete the study: The reason for study discontinuation was concomitant cerebral infarction after the second cycle of chemotherapy and sudden death due to asphyxia of uncertain etiology after the first cycle of chemotherapy. None of them was considered by the investigators to be treatment-related and all of these patients were determined to be off the study. Patients who received at least two cycles of chemotherapy were evaluated for efficacy and safety in the intention-to-treat analysis. Patients characteristics at baseline are shown in Table 1. Mean relative dose intensities were 91.2% for gemcitabine and 98.9% for oxaliplatin in the study population.

Efficacy and survival

Response data are summarized in Table 2. The general objective response was 18.9%. One complete response

Table 1 Patients characteristics

Characteristic	Number of patients (n = 53)	(%)
Sex		
Male	24	45
Female	29	55
Age, years		
Median	61	
Range	40–80	
ECOG PS		
0	4	7.5
1	46	86.8
2	3	5.7
Primary cancer site		
Intrahepatic biliary cancer	20	37.7
Extrahepatic biliary cancer	11	20.8
Gallbladder cancer	22	41.5
Metastatic sites		
Liver	44	83.0
Lymph nodes	40	75.5
Lung	8	15.1
Bone	6	11.3
Omentum	4	7.5
Adrenal gland	3	5.7
Peritoneum	3	5.7
Others	6	11.3
Numbers of metastasis		
1	14	26.4
2	18	34.0
3	19	35.8
4	2	3.8
Numbers of Chemotherapy		
Median	4	
Range	2–7	

ECOG PS Eastern Cooperative Oncology Group performance status

Table 2 Response and Survival

Treatment response	Number of patients ($n = 53$)	%
	53	100
Complete response (CR)	1	1.9
Partial response (PR)	9	17.0
Stable disease (SD)	27	50.9
Progressive disease (PD)	16	30.2
Objective response[a]	10	18.9
Disease control rate[b]	37	69.8
Median PFS (months)	4.8 (3.1–6.5, 95% CI)	
Median OS (months)	8.3 (5.8–10.8, 95% CI)	

[a] Including CR and PR

[b] Including CR, PR and SD

Table 3 Response and CA19-9 reduction

	Response (+)	Response (−)	p value
CA19-9 reduction <50%	5 (14.7%)	29 (85.3%)	0.048
CA19-9 reduction ≥50%[a]	5 (45.5%)	6 (54.5%)	

[a] Achieved more than 50 percent reduction of serum CA19-9 after chemotherapy

(CR) was observed (1.9%). Partial response (PR) and stable disease (SD) were observed in 9 (17%) and 27 (50.9%) patients, respectively. Disease control rate (DCR), response rate comprising SD, was achieved in 69.8% of all patients. Median PFS was 4.8 months (3.1–6.5, 95% CI) and median OS was 8.3 months (5.8–10.8, 95% CI) (Table 2). At the end-point of this study, three patients were still alive. On univariate analysis, median PFS were longer for patients without lymph node (LN) metastasis (7.0 vs. 3.3 months, $p = 0.006$), patients with objective response (6.5 vs. 3.5, $p = 0.039$) and patients with clinical benefit (6.3 vs. 1.5, $p = 0.001$), respectively. Median OS were significantly longer for patients without LN metastasis (13.3 vs. 7.0 months, $p = 0.021$), clinical benefit (11.3 vs. 4.8, $p = 0.001$) and ≥10% decline of CA-19-9 (11.8 vs. 7.3, $p = 0.021$), respectively. Extent of CA-19-9 decline correlates with clinical response in that patients with response showed a tendency of ≥50% decline of CA-19-9 (Table 3). On multivariate analysis, the existence of LN metastasis adversely affects median PFS (hazard ratio 0.402, 95% CI, 0.198–0.813; $p = 0.011$). Median OS were significantly affected by clinical benefit (hazard ratio 0.145, 95% CI, 0.059–0.353; $p = 0.001$), and CA-19-9 decline (>10%) (HR 0.376, 95% CI, 0.186–0.761; $p = 0.007$) (Table 4). No significant difference was evident between gall bladder cancer and cholangiocarcinoma, as determined by criteria for response rate and survival.

Safety

Grade 3/4 hematologic toxicities were observed in 47% of patients while Grade 3/4 nonhematologic toxicities were observed in 3.8% of patients: Neutropenia (33.9%) including 2 febrile episodes (3.8%) was the most frequent grade 3/4 hematologic toxicity; overall, emesis of all grades (75.5%) was the most frequent side effects despite of preventive measures. Anemia (75.5%), thrombocytopenia (56.6%), alopecia (37.7%), asthenia (32.1%), mucositis (18.9%) and diarrhea (18.9%) were observed. All of these toxicities were grade 1/2 in severity and reversible. Peripheral sensory neuropathy was observed in 37.7% of patients. The majority of neuropathy was mild (grade 1, 35.8%) and was dose cumulative. Results are summarized in Table 5.

Discussion

To date, gemcitabine based chemotherapy is the only regimen showing significant efficacy to prolong survival and relieve symptoms. By far, only small numbered, single center phase II trials have assessed the efficacy and toxicities of gemcitabine-based regimens showing variable response rates (13–50%) and overall survival (5–14 months) [18].

Table 4 Multivariate analysis of prognostic factors for survival

Factor	HR for PFS (95% CI)	P value[a]	HR for OS (95% CI)	P value[a]
LN metastases				
Yes	0.402 (0.198–0.813)	0.011	0.456 (0.207–1.005)	0.051
No				
Clinical benefit				
CR/PR/SD			0.145 (0.059–0.353)	0.001
PD				
≥10% decline of serum CA19-9[b]				
Yes			0.376 (0.186–0.761)	0.007
No				

HR hazard ratio

[a] Forward stepwise (conditional LR) method of Cox proportional hazard regression model

[b] Achieved more than 10 percent reduction of serum CA19-9 after chemotherapy

Table 5 Toxicity

	Number of patients (%)			
	Grade I	Grade II	Grade III	Grade IV
Hematological				
Neutropenia	3 (5.7)	12 (22.6)	12 (22.6)	6 (11.3)
Febrile neutropenia	1 (1.9)	0 (0)	2 (3.8)	0 (0)
Thrombocytopenia	14 (26.4)	12 (22.6)	3 (5.7)	1 (1.9)
Anemia	21 (39.6)	18 (34.0)	1 (1.9)	0 (0)
Non-hematoloical				
Emesis	32 (60.4)	7 (13.2)	1 (1.9)	0 (0)
Diarrhea	6 (11.3)	3 (5.7)	1 (1.9)	0 (0)
Mucositis	9 (17.0)	1 (1.9)	0 (0)	0 (0)
Fatigue/Anorexia	11 (20.8)	6 (11.3)	0 (0)	0 (0)
Neuropathy	19 (35.8)	1 (1.9)	0 (0)	0 (0)
Alopecia	16 (30.2)	4 (7.5)	0 (0)	0 (0)

Reported higher response rate in small studies are mostly unconfirmed yet. Median survival and overall response rate achieved by our patients were 8 months and 19%, respectively. These data were somewhat lower than previous single center trial results but in the range of most other studies investigating combination chemotherapy for BTC and especially similar with a recently reported multicenter trial data [2]. Taking into account this recently published data, two sequential results (Table 6) could be regarded as an acceptable consensus on the therapeutic potentials of GEMOX combination.

In this study, we conducted subgroup analysis to assess whether the existence of LN metastasis has an influence on patient's survival. Multivariate analysis in this study showed at least three facts. First, patients with LN metastatic foci have significantly shorter PFS compared with patients with no LN metastasis. At this point in time, this data suggest that nodal metastasis could be a surrogate marker of systemic disease and that their existence is to alter potential benefit of chemotherapy. This suggestion is somewhat different from other gastrointestinal solid tumors, in which distant metastasis is much more a fatal marker for survival. Status of LN metastasis is worthy to be taken into account as a prognostic factor for further study in addition to performance status, which has been established as a firm prognostic factor.

Second, although the statistical power is low, this study supports the concept that tumor marker of CA-19-9 could be helpful to determine tumor response and survival in a substantial population of patients.

Third, another important finding to outline is that response rate comprising CR and PR is not good prognostic marker for survival in this study. Rather, disease control rate comprising stable disease is a significant surrogate marker for survival in this setting. Disease stabilization with GEMOX treatment translated into a clinical benefit as better PFS and OS.

We observed no difference in survival and toxicity between GBC and cholangiocarcinoma. The reported efficacy here, especially for GBC, differed from previous studies of GEMOX in that GBC is generally considered worse than cholangiocarcinoma [2, 6]. Planned randomized studies should include these two tumor types by stratification to elucidate the possible differences of clinical behavior.

The GEMOX combination here was well tolerated. The toxicity profile of this study was comparable with other

Table 6 Comparison of similar studies

	Chemotherapy	*N*	RR (%)	PFS (mo)	OS (mo)	Gr3-4 toxicity
Andre [3]	G 1,000 mg/m^2 D1[a] O 100 mg/m^2 D1 Every 2 weeks	56	28.7	4.8	11.5	Neutropenia, anemia thrombocytopenia
Harder [8]	G 1,000 mg/m^2 D1,8,15[b] O 100 mg/m^2 D1,15 Every 4 weeks	31	26	6.5 TTP	11	Thrombocytopenia, anemia leucopenia, neuropathy
Manzione [12]	G 1,000 mg/m^2 D1[b] O 100 mg/m^2 D2 Every 2 weeks	34	41	9 TTP	10	Thrombocytopenia, leucopenia, neuropathy
Comparison of similar studiesAndre [2]	G 1,000 mg/m^2 D1[a] O 100 mg/m^2 D2 Every 2 weeks	70	14.9	3.4	8.8	Neutropenia, anemia, thrombocytopenia ALT, pain
Present study 2009	G 1,000 mg/m^2 D1,8[c] O 100 mg/m^2 D1 Every 3 weeks	53	18.9	4.8	8.3	Neutropenia, anemia thrombocytopenia emesis, diarrhea

RR response rate, *PFS* progression free survival, *TTP* time to progression, *OS* overall survival, *G* gemcitabine, *O* oxaliplatin

[a] Gemcitabine 1,000 mg/m^2 as a 10 mg/m^2/min infusion (100 min infusion)

[b] 30 min infusion

[c] 60 min infusion

studies using GEMOX. A few of grade 3/4 adverse reactions were reported, although most patients experienced grade 1/2 toxicities. The most frequent toxicities were myelosuppression and asthenia and mostly mild or moderate in severity. Sensory peripheral neuropathy, concerned with oxaliplatin use was less observed than in previous reports. After chemotherapy discontinued, there was a fast resolution of treatment-related symptoms and signs. All of the deaths were attributed to the underlying malignancy.

Based on the current study and others, gemcitabine and oxaliplatin are important components of chemotherapy regimen but the potential benefit of the combination remains modest. By far, the role of platinum drugs in combination chemotherapy is not decisive yet and need to be determined by large phase III trials comparing gemcitabine alone with gemcitabine-based combination chemotherapy.

Evidence of some oncogenic mutations including K-ras and EGFR offers genetic basis for tailored regimens with targeted agents and preliminary data suggest targeted agents have activity in BTC. These cytostatic targeted agents are worthy to be explored in combination with conventional regimens.

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