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ORIGINAL ARTICLE

Phase II trial of gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas

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Abstract
Objectives The aim of this phase II study was to evaluate the response rate to gemcitabine combined with cisplatin in patients with locally advanced, metastatic or recurrent biliary tract cancer who had received no prior chemotherapy.
Methods The treatment consisted of cisplatin 70 mg/m^2 in intravenous infusion followed by gemcitabine 1,250 mg/m^2 in 30-min intravenous infusion on days 1 and 8, repeated every 3 weeks until disease progression, unacceptable toxicity, patient's refusal or up to 8 cycles.
Results Thirty-nine patients with advanced biliary cancer were enrolled between March 2003 and August 2003. Fourteen patients (40%) had gall bladder cancer and 20 patients (57%) had cholangiocarcinoma. Thirty-two patients (91%) had metastatic disease at study entry with liver being the most commonly involved site of metastasis. About 84.5 and 94.2% of the initially planned dose were administered for gemcitabine and cisplatin, respectively. In the ITT population ($n = 35$), six partial responses were observed for an objective response rate of 17.1% (95% CI; 4.7–29.6%). Ten patients (28.6%) had stable disease, 16 (45.7%) progressed, and three (8.6%) were not evaluable. For the 35 patients in the ITT population, the median overall survival time was 8.6 months (95% CI; 6.1–10.4 months). The median time to disease progression was 3.2 months (95% CI; 2.3–4.9 months) and the median time to treatment failure was 3.1 months

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(95% CI; 1.9–4.1 months). Among the six tumor responders, the median duration of tumor response was 7.3 months (95% CI; 5.6–11.0 months). The most common grade 3/4 maximum toxicities were nausea (3.4%) and vomiting (2.7%).

Conclusion The combination chemotherapy with gemcitabine and cisplatin in this trial demonstrated moderate antitumor activity with favorable toxicity profile.

Introduction

Biliary tract carcinoma (BTC) is rare in the West, but not uncommon in Asian countries including Korea and Japan. There are ~3,500 patients who are newly diagnosed of BTC each year and accounts for 6% of all cancer deaths in Korea [1]. BTCs are highly lethal cancers with 1-year survival rate of 25% [2]. Although surgery remains to be the only curative treatment for BTC, most patients are candidates for palliative chemotherapy at initial presentation [3–6]. Therefore, the exploration of an optimal regimen for standard first-line chemotherapy for BTC is imperative in order to improve survival in these patients. However, because of the low incidence of BTC, clinical trials are difficult to conduct in these patients hampering the evaluation of new drugs.

Gemcitabine is a nucleoside analogue, which requires intracellular phosphorylation by the enzyme deoxycytidine kinase and converts it to the active difluorodeoxycytidine diphosphate (dFdCDP) and triphosphate (dFdCTP) forms. The dFdCTP competes with deoxycytidine triphosphate for incorporation in DNA, which results in inhibition of DNA synthesis. Since gemcitabine is the only drug so far which has proven survival benefit and clinical benefit response in advanced pancreatic cancer patients, it also has been studied in advanced BTC [7]. Gemcitabine has demonstrated antitumor activity as monotherapy in Phase II trials in BTC patients with response rates ranging from 22 to 36% [8–10]. Preclinical studies reported synergistic activity of gemcitabine and cisplatin by decreasing in repair of DNA-platinum adducts [11, 12]. Based on preclinical studies, and well-established activity of the combination in non-small cell lung cancer, several small-scaled phase II trials were conducted in patients with advanced BTCs. Carraro et al. reported preliminary results of a combination regimen of gemcitabine 1,000 mg/m^2 and cisplatin 30 mg/m^2 both given on days 1, 8, 15 of a 28-day cycle in 11 patients and the response rate was 50% [13]. In a larger phase II trial, Doval et al. enrolled 30 chemotherapy-naïve patients and administered gemcitabine 1,000 mg/m^2 on days 1 and 8 and cisplatin 70 mg/m^2 on day 1, every 3 weeks [14]. Their preliminary report indicated that the overall response rate was 53%, which decreased to 36.6% in final analysis. Toxicities were generally acceptable with 16.6% of patients experiencing grade 3 or 4 neutropenia.

The primary objective of this multicenter phase II study was to evaluate the response rate to gemcitabine combined with cisplatin in patients with locally advanced, metastatic or recurrent BTC who had received no prior chemotherapy.

Patients and methods

Eligibility

Eligibility criteria for study entry were as follows: (1) pathologically proven adenocarcinoma of the gall bladder, intra/extrahepatic bile ducts or papilla of Vater; (2) locally advanced or metastatic disease not amenable to curative surgical resection; (3) bidimensionally measurable lesion (≥2.0 cm in diameter by computerized tomography (CT) or magnetic resonance imaging (MRI) or palpable lesion with ≥2.0 cm in diameter); (4) no prior chemotherapy for advanced disease; (5) Eastern Cooperative Oncology Group (ECOG) performance status ≤2; and (6) adequate organ functions (WBC 3.5–12.0 × 10^9 per liter, absolute neutrophil count ≥1.5 × 10^9 per liter, platelet count ≥100 × 10^9 per liter, hemoglobin of ≥9 g/dl, AST and ALT ≤5 × upper limit of normal (ULN) and bilirubin ≤2 × ULN, creatinine ≤1.5 × ULN, an calculated creatinine clearance ≥60 ml/min. Patients with poorly controlled heart failure, angina pectoris or arrhythmia or acute myocardial infarction within 6 months from study enrollment, active infection, serious concomitant disorders, symptomatic brain metastasis or second primary malignancy that is clinically detectable at the time of study entry were excluded from the study. All patients provided written informed consent. The protocol and the informed consent form were approved by the Institutional Review Board.

Treatment

The treatment consisted of cisplatin 70 mg/m^2 in intravenous infusion followed by gemcitabine 1,250 mg/m^2 in 30-min intravenous infusion on days 1 and 8, repeated every 3 weeks for up to 8 cycles unless disease progression, unacceptable toxicity, or patient's refusal to continue therapy. Cisplatin was preceded by prehydration and antiemetic prophylaxis as per institutional practice. Adverse events were recorded according to the National Cancer Institute Common Toxicity Criteria (Version 2).

Dose adjustments were based on the worst toxicity observed in the preceding cycle. Any patient who required a dose reduction for subsequent cycles continued to receive a reduced dose for the remainder of the study. Any patient with two prior dose reductions who experienced a toxicity

that caused a third dose reduction was to be discontinued from study treatment. ANC $\geq 1.5 \times 10^9$ per liter and platelets $\geq 100 \times 10^9$ per liter prior to each cycle were required. If grade 4 neutropenia lasted for more than 5 days or was associated with febrile episode (≥ 38.5°C), doses of gemcitabine and cisplatin were reduced by 20%. If platelet count was $<50 \times 10^9$ per liter or ANC $<0.75 \times 10^9$ per liter on day 8, gemcitabine was omitted for the cycle. If peripheral neuropathy of NCI-CTC grade 2 occurred during treatment, the dose of cisplatin was reduced by 20% in subsequent cycles. If patient still had good performance status when disease progression was documented, second-line chemotherapy was administered at the discretion of the treating oncologist.

Assessments

Prior to starting study treatment, the following assessments were performed for each patient: radiologic imaging studies (CT or MRI scan) within 2 weeks before treatment, medical history and physical examination within 4 weeks of treatment, complete blood count, liver, renal and bone marrow function tests within 1 week before treatment. Prior to each cycle, all patients were assessed with limited medical history and physical examination, performance status evaluation, complete blood count, and renal and hepatic function tests. Tumor measurements by imaging studies were performed every 2 cycles and reviewed by independent radiologic expert panel. All tumor responses were confirmed within 4 weeks of the first response documentation. After the completion of chemotherapy, assessments for disease progression were performed every 6 weeks until disease progression or 12-month post-study enrollment or death.

Statistical considerations

The primary endpoint was response rate and secondary endpoints were overall survival (OS), duration of response, and time to progression (TTP). The actual dose intensity (DI) was calculated using the following formula: actual DI = total dose given during the study/duration in weeks, where the end of treatment was considered 21 days after Day 1 of the last cycle of chemotherapy. The relative DI was calculated as the ratio of the actual DI to the planned DI in the protocol. Descriptive statistics were reported as proportions and medians. Kaplan-Meier estimates were used in the analysis of time-to-event variable and the 95% confidence interval (CI) for the median time to event was computed.

A sample size of 32 was required to accept the hypothesis that the true response rate was greater than 27% with 80% power, and to reject the hypothesis that the response rate was less than 10% with 5% significance. Assuming that 15% of patients were inassessable, a total of 38 patients were planned to be accrued for the study.

Results

Patient characteristics

Thirty-nine patients with advanced biliary cancer were enrolled between March 2003 and August 2003. Of the 39 patients, four patients were withdrawn from the study due to the violation of inclusion and exclusion criteria. Demographics and baseline characteristics are listed in Table 1. Fourteen patients (40%) had gall bladder cancer and 20 patients (57%) had cholangiocarcinoma. Thirty-two patients (91%) had metastatic disease at study entry with liver being the most commonly involved site of metastasis. Majority of patients had good performance status at start of therapy (ECOG ≤ 1, 91%), and median age was 60 years.

Table 1 Patient characteristics

	ITT Population ($n = 35$)
Sex, number (%)	
Male	23 (65.7)
Age (years)	
Median (range)	60 (36–68)
Performance status	
0	7 (20.0)
1	25 (71.4)
2	3 (8.6)
Primary tumor site	
Gallbladder	14 (40.0)
Intrahepatic bile-duct	18 (51.4)
Extrahepatic bile-duct	2 (5.7)
Papilla of Vater	1 (2.9)
Stage of disease at study entry	
Stage β/IV	3/32
Sites of metastases	
Liver	29 (82.9)
Lung	5 (14.3)
Lymph nodes, regional	22 (62.9)
Other	13 (37.1)
Prior surgery	
Palliative	3 (8.6)
Curative	5 (14.3)
Grade of histopathological diagnosis	
Poorly differentiated	7 (20.0)
Moderately differentiated	10 (28.6)
Well differentiated	8 (22.9)
Unknown	10 (28.6)

Treatment outcome

A median of 4 cycles per patient was administered with a range from 1 to 8 (Table 2). Of the 148 cycles administered, 8 cycles of gemcitabine and 19 cycles of cisplatin were reduced due to adverse effects with neutropenia being the most common event for dose reductions. About 84.5 and 94.2% of the initially planned dose were administered for gemcitabine and cisplatin, respectively. In the ITT population ($n = 35$), six partial responses were observed for an objective response rate of 17.1% (95% CI; 4.7–29.6%, Table 3). Ten patients (28.6%) had stable disease, 16 (45.7%) progressed, and three (8.6%), who were lost to follow up were not evaluated. For the 35 patients in the ITT population, the median OS time was 8.6 months (95% CI; 6.1–10.4 months, Fig. 1). The proportion of patients surviving for at least 6, 9, and 12 months was 68.6 ($n = 24$), 48.6 ($n = 17$), and 31.4% ($n = 11$), respectively. The median time to disease progression was 3.2 months (95% CI; 2.3–4.9 months) and the median time to treatment failure was 3.1 months (95% CI; 1.9–4.1 months). The main reason for treatment failure during the study phase and the follow up period was progression of the disease (74.3%; $n = 26$). Among the six tumor responders, the median duration of tumor response was 7.3 months (95% CI; 5.6–11.0 months).

Toxicity profile

Following a total of 148 cycles (median 4 cycles; range 1–8), the most common grade 3/4 maximum CTC hematologic toxicities were neutropenia (53/148 cycles, 35.8%) and thrombocytopenia (26/148 cycles, 17.6%) without treatment-related mortality (Table 4). The most common grade 3/4 maximum CTC non-hematologic toxicities were nausea (5/148 cycles, 3.4%) and vomiting (4/148 cycles, 2.7%). The most frequently reported serious adverse event during treatment that was potentially related to the study drug was thrombocytopenia (3 of 39 patients; 7.7%). Of the 616 adverse events, nausea (64.9%) and anorexia (50.0%) were the most common.

Table 3 Response rate

	Number of patients (%)		
	Gallbladder cancer	Others	Total
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	4 (28.6)	2 (9.5)	6 (17.1)
Stable disease	2 (14.3)	8 (38.1)	10 (28.6)
Progressive disease	8 (57.1)	8 (38.1)	16 (45.7)
Not evaluated	0 (0.0)	3 (14.3)	3 (14.3)
Response rate [95% CI]	28.6% [4.9–52.2]	9.5% [−3.0 to 22.1]	17.14% [4.7–29.6]

Influential factors for response

Clinical variables included in the analysis were age, gender, performance status (ECOG), surgery, radiotherapy and

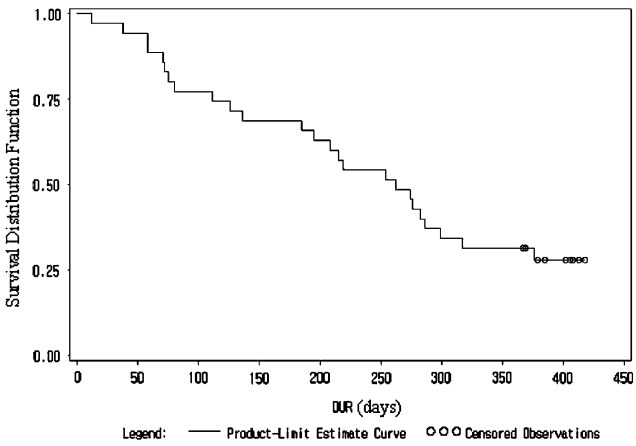

Fig. 1 Kaplan-Meier curve of survival

Table 2 Drug delivery

	Gemcitabine ($n = 39$)		Cisplatin ($n = 39$)
	Day 1	Day 8	
Total number of treatment cycles administered	148	128	148
Actual dose intensity (median, mg/m^2/week)	704.0		22.0
Relative dose intensity (%)	84.5		94.2
Total number of reductions	8(100.0)		19(100.0)
Reasons for dose reduction			
Neutropenia	2(25.00)	17(89.47)	2(22.22)
Febrile neutropenia	1(12.50)	0	1(11.11)
Thrombocytopenia	4(50.00)	2(10.53)	4(44.44)
Neurotoxicity	0	0	1(11.11)
Nephrotoxicity	1(12.50)	0	1(11.11)

Table 4 Grade 3 or 4 adverse events

Toxicity	Toxicity per cycle (n = 148)	
	n	Avg%
Hematologic		
Neutropenia	53	35.8
Thrombocytopenia	26	17.6
Anemia	10	6.8
Febrile neutropenia	2	1.4
Non-hematologic		
Nausea	5	3.4
Vomiting	4	2.7
Constipation	3	2.0
Alanine aminotransferase increased	2	1.4
Cerebral infarction	1	0.7
Creatinine renal clearance decreased	1	0.7
Hyperbilirubinemia	1	0.7
Peripheral neuropathy	0	0

Avg % = (number of cycles with CTC grade 3/4 for all patients/total 148 cycles for all patients) × 100

primary tumor site. For tumor site, gallbladder subgroup had tendency towards higher response rate than other sites with adjusted OR of 1.8 (95% CI, 0.20–15.74, $P = 0.615$) indicating that patients with gallbladder cancer were more likely to respond to chemotherapy by 1.8-fold. Other factors such as age, prior surgery or gender were not significantly predictive of treatment response.

Discussion

This multicenter phase II study of gemcitabine and cisplatin demonstrated a response rate of 17.1% with disease stabilization in 28.6% resulting in an overall disease control rate of 45.7%. The response rate obtained in the trial was somewhat lower than those reported in previous gemcitabine-based combination phase II trials, which ranged between 34 and 50% [14–18]. Despite of low response rate, the median OS time (8.6 months) was comparable to other studies, which ranged from 7.0 to 11.3 months [14–18]. The discrepancy between the response rate and OS time potentially implicates the limitation of conventional method such as RECIST as an assessment tool. The extensive desmoplasia and peritumoral inflammation in biliary tract cancers may be attributable to this discrepancy, underscoring the development of surrogate biomarkers in clinical trials. Recently, a potential role of CA19-9 as a surrogate marker has been suggested in BTCs [17] in addition to pancreatic cancer [19], although further validation is needed for routine use in clinical practice.

Another factor that may account for the lower response rate in the trial may be different inclusion criteria among trials. In particular, the proportions of gallbladder cancer and cholangiocarcinoma vary in different trials. Few trials [14, 18] included only gallbladder cancers where as other trials enrolled cholangiocarcinomas [15, 16]. Forty percent of the enrolled patients were gallbladder cancers in this trial. As demonstrated in our trial and others, gallbladder cancer may have different sensitivity to chemotherapy as compared to cholangiocarcinoma, which needs to be validated in larger trials. The subtypes should be included in the stratification scheme when designing randomized studies in BTCs, however.

The combination regimen of gemcitabine and cisplatin showed favorable toxicity profile. The most common grade 3/4 CTC hematologic toxicities were neutropenia (35.8%) and thrombocytopenia (17.6%) without treatment-related mortality. The most common grade 3/4 maximum CTC non-hematologic toxicities were nausea (3.4%) and vomiting (2.7%), which were generally manageable. There was no neutropenic fever recorded in the trial. The incidence of grade 3/4 toxicities was comparable to previous studies.

There is no standard chemotherapy regimen for BTCs as of to date. Moreover, the superiority of gemcitabine-based combination therapy has not been shown yet. Because of the peculiar mechanism of action and its non-overlapping toxicity with other antitumor drugs, gemcitabine is definitely an attractive option for trials in combination with others. Recently, gemcitabine has shown promising antitumor activity when combined with capecitabine (median OS, 11.3–14 months) and with oxaliplatin (median OS time, 14 months) [20–22]. Direct comparison of survival time is not justifiable especially in small phase II trials, however.

In conclusion, the combination chemotherapy with gemcitabine and cisplatin in this trial demonstrated moderate antitumor activity with favorable toxicity profile. Based on recent clinical trials, gemcitabine is one of most studied agents and should be considered as an essential chemotherapeutic agent in the treatment of advanced biliary tract cancer, therefore it is also worthy to evaluated the new methods of administering gemcitabine like a fixed dose rate that showed additional improvement in activity as in the treatment of advanced pancreatic cancer.

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