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ORIGINAL ARTICLE

Multicenter, phase II study of gemcitabine and S-1 combination chemotherapy in patients with advanced biliary tract cancer

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Abstract
Purpose To evaluate the efficacy and safety of gemcitabine and S-1 combination chemotherapy in patients with advanced biliary tract cancer.
Methods Patients with a measurable lesion and no previous history of chemotherapy or radiotherapy were enrolled. Gemcitabine was administered intravenously at a dose of 1,000 mg/m^2 over 30 min on day 1 and 15, repeated every 4 weeks. S-1 was administered orally at a dose of 40 mg/m^2 b.i.d. on days 1–14. Tumor response was assessed every two cycles using Response Evaluation Criteria in Solid Tumors criteria.
Results As much as 35 patients were enrolled between December 2006 and July 2008; 14 patients (40%) with gallbladder cancer and 14 (40%) with intrahepatic cholangiocarcinoma were included and 7 patients (20%) had received previous surgical resection. The overall response rate was 34.3% and the overall disease control rate was 82.9%. The median overall survival time was 11.6 months (95% CI, 7.3–15.6 months), and the median time to progression was 5.9 months (95% CI, 4.0–7.7 months). The grade 3/4 toxicities were leucopenia (23%), neutropenia (34%), anemia (20%), thrombocytopenia (6%) and anorexia (3%).
Conclusions Gemcitabine and S-1 combination chemotherapy has promising efficacy and good tolerability in patients with advanced biliary tract cancer.

Keywords Biliary tract cancer · Gemcitabine · S-1 · Chemotherapy

Introduction

Advanced biliary tract cancer (BTC) carries a poor prognosis, and standard chemotherapy for its treatment is yet to

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be well established [1]. Only several small phase II studies have been reported because of the rarity of BTC. Pooled analyses of these small number of clinical trials reveal that gemcitabine and cisplatin combination chemotherapy have a superior tumor response for advanced BTC [2, 3].

In 2009 at the annual meeting of the American Society of Clinical Oncology (ASCO), a prospective multicenter, phase III study of gemcitabine and cisplatin combination chemotherapy versus single-agent gemcitabine (ABC-02 study) was reported [4]. This study was the largest clinical trial conducted in this field, which included 410 patients. The median survival times of gemcitabine and cisplatin combination chemotherapy and single-agent gemcitabine were 11.7 and 8.3 months, respectively ($P = 0.002$). From the report of ABC-02 study, gemcitabine and cisplatin combination chemotherapy will become a standard of care for the treatment of advanced BTC. Additionally, the advantage of gemcitabine and cisplatin combination chemotherapy against single-agent gemcitabine was confirmed by a randomized phase II study conducted in Japan (BT-22 study) [5].

Recently, a favorable tumor response was observed by the gemcitabine-combination chemotherapy with oxaliplatin or capecitabine in several phase II studies [6–12]. Although the combination of gemcitabine and oxaliplatin is a good treatment option for advanced BTC, the adverse effect of peripheral sensory neurotoxicity might decrease the patient's quality of life; the rate of grade 3/4 neurotoxicity was reported as 6–19% [6–9]. The combination with capecitabine also has a possible disadvantage of inducing hand–foot syndrome; the rate of grade 2/3 hand–foot syndrome was reported as 9–29% [10, 11].

S-1 is an oral fluoropyrimidine prodrug, which is widely used for various solid tumors. S-1 monotherapy showed favorable outcomes with mild toxicity for advanced BTC [13–15]. Recently, combination chemotherapy using gemcitabine and S-1 have showed good anti-tumor effect and tolerability in patients with advanced pancreatic cancer and non-small cell lung cancer [16–21], whereas no clinical study has investigated on advanced BTC. We therefore conducted a multicenter, phase II study to evaluate the efficacy and safety of gemcitabine and S-1 combination chemotherapy in patients with advanced BTC.

Patients and methods

This multicenter, phase II study was an open-label, single-arm study that was conducted in 12 institutions in Japan. The protocol was approved by the institutional review board. Informed consent was obtained from each participant.

Eligibility criteria

Patients who had advanced BTC that was not amenable to potentially curative surgery or refractory to surgery were eligible if they met the following criteria: all enrolled patients had pathologically confirmed BTC and unidimensionally measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) [22]; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and adequate bone marrow function (white blood count $>3{,}000/mm^3$, hemoglobin >9.0 g/dL and platelet count $>100{,}000/mm^3$), liver function [total bilirubin <3 times the upper limit of normal (ULN) and aspartate/alanine transaminases <5 times ULN] and renal function (creatinine <1.2 mg/dL or creatinine clearance >50 mL/min). In patients with obstructive jaundice, total serum bilirubin was required to be within three times the ULN after biliary drainage.

Exclusion criteria included age <20 years, a prior history of chemotherapy or radiotherapy, uncontrolled infection, active ulcer of the gastrointestinal tract, gastrointestinal obstruction compromising oral ingestion, pregnancy or lactation, a history of drug hypersensitivity, active concomitant malignancy and concurrent severe medical conditions.

Treatment

Gemcitabine was given intravenously at 1,000 mg/m^2 over 30 min on days 1 and 15, repeated every 4 weeks. S-1 was administered orally twice daily from day 1 to 14, followed by a 2-week rest. Three doses of S-1 were established according to body surface area (BSA) as follows: BSA $< 1.25\ m^2$, 80 mg/day; $1.25\ m^2 \leq$ BSA $< 1.5\ m^2$, 100 mg/day; and BSA $\geq 1.5\ m^2$, 120 mg/day. Dose reduction was based on adverse effects graded according to National Cancer Institute Common Toxicity Criteria version 3.0. In case of grade 3/4 hematological toxicity or grade 2 or higher non-hematological toxicity, treatment was temporarily suspended. After confirming the resolution to a grade 1 toxicity level or lower, treatment was restarted at a reduced dose. At first, S-1 was reduced to the following doses: BSA $<1.25\ m^2$, 60 mg/day; $1.25\ m^2 \leq$ BSA $< 1.5\ m^2$, 80 mg/day; and BSA $\geq 1.5\ m^2$, 100 mg/day. If the toxicity occurred in spite of S-1 reduction, gemcitabine was reduced to 800 mg/m^2. If further toxicity was experienced, the dose was reduced again. S-1 was reduced to the following doses: BSA $<1.25\ m^2$, 40 mg/day; $1.25\ m^2 \leq$ BSA $< 1.5\ m^2$, 60 mg/day; and BSA $\geq 1.5\ m^2$, 8 mg/day, and gemcitabine was reduced to 600 mg/m^2. If further dose reduction was needed, the study treatment was put on hold. No dose re-escalation was allowed. The study

treatment was continued until disease progression, unacceptable toxicity or patient refusal occurred.

Response and toxicity assessment

Pretreatment evaluation included medical history and physical examination, complete blood count, serum biochemical tests, urinalysis and echocardiogram. The ECOG performance status, and laboratory tests including complete blood counts and serum biochemical tests were checked every 2 weeks. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were measured at the inclusion of the study and at day 1 of each cycle. Pretreatment evaluation using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was conducted within 4 weeks before the patient's enrollment. Tumor response was assessed every two cycles. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0.

Statistical analysis

The primary end point was the objective response rate. The secondary end points were time to progression, overall survival and toxicity. The sample size was calculated to reject a 20% response rate in favor of a target response rate of 40%, with a significance level of 0.05 and a power of 80% using Simon's two-stage design [23]. In the initial stage, 18 assessable patients were enrolled. If only four or fewer patients had an objective response, the study was terminated for lack of efficacy. Otherwise, an additional 15 patients were enrolled to achieve a target sample size of 33 assessable patients. If 11 or more objective responses were observed among all 33 assessable patients, the regimen was considered worthy of additional evaluation.

The objective response rate was evaluated according to RECIST criteria [22]. Patients who stopped the study treatment within the first 15 days of the first cycle were deemed "not evaluable" for tumor response. Time to progression and overall survival were calculated using the Kaplan–Meier method. Time to progression was calculated from the start of the treatment to the first date of documented disease progression. Overall survival was defined as the time from initiation of therapy to the final follow-up, or else until death from any cause. The final analysis was based on follow-up information received until January 2009.

All analyses were conducted based on the intention-to-treat principle. The JMP 7.0.1 statistical software program (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Patient characteristics

As much as 35 patients were enrolled between December 2006 and July 2008. Patient characteristics are listed in Table 1. The median age was 67 years (range 49–79 years) and 22 patients (63%) were men. The primary cancer site was the gallbladder in 14 patients (40%), the intrahepatic bile duct in 14 patients (40%) and the extrahepatic bile duct in 6 patients (17%). Seven patients (20%) had previously

Table 1 Patient characteristics ($n = 35$)

Age (years)	
Median	67
Range	49–79
Gender	
Male	22 (63%)
Female	13 (37%)
ECOG performance status	
0	16 (46%)
1	18 (51%)
2	1 (3%)
Location of primary tumor	
Gallbladder	14 (40%)
Intrahepatic bile duct	14 (40%)
Extrahepatic bile duct	6 (17%)
Ampulla of Vater	1 (3%)
Disease status	
Locally advanced	3 (9%)
Metastatic	25 (71%)
Recurrent	7 (20%)
Metastatic sites	
Liver	16 (46%)
Lung	9 (26%)
Lymph node	26 (74%)
Peritoneum	3 (9%)
Bone	3 (9%)
CA19-9 (U/ml)	
Median	155
Range	1–311276
CEA (ng/ml)	
Median	6.4
Range	0.9–471.5
BSLD (cm)	
Median	9.3
Range	1.5–26.0

ECOG Eastern Cooperative Oncology Group, *CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *BSLD* baseline sum of longest diameter

received surgical resection with curative intent. The median baseline sum of longest diameter (BSLD) was 9.3 cm (range 1.5–26.0 cm). As subset analyses, the median BSLD of gallbladder cancer, intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma were 10.1 cm (range 3.0–19.0 cm), 10.2 cm (range 3.0–26.0 cm) and 3.8 cm (range 1.5–8.3 cm), respectively. The median duration of follow-up was 9.3 months. A total of 15 patients (43%) were still alive at the time of this analysis.

Efficacy

In the initial stage of Simon's two-stage design, six patients had an objective response [two patients showed complete response (CR) and four showed a partial response (PR)]. Overall, two patients (6%) achieved CR and ten (29%) showed PR, with an overall objective response rate of 34.3% (Table 2). Stable disease was observed in 17 patients (49%), with an overall disease control rate of 82.9%.

The median overall survival time was 11.6 months (95% CI, 7.3–15.6 months) and the median time to progression was 5.9 months (95% CI, 4.0–7.7 months) (Fig. 1). Six-month progression-free survival and 1-year overall survival rates were 48.8 and 44.4%, respectively. The median time to progression of gallbladder cancer, intraheptic cholangiocarcinoma and extrahepatic cholangiocarinoma were 5.7, 6.3 and 6.1 months, respectively. The median overall survival times of gallbladder cancer and intrahepatic cholangiocarcinoma were 9.1 and 10.3 months, respectively. As for extrahepatic cholangiocarcinoma, the median overall survival is not available because five of the six patients (83%) are still alive.

Toxicity

In total, 231 cycles of gemcitabine and S-1 combination chemotherapy were delivered, with a median of six cycles per patient (range 1–23 cycles). Two patients suspended the study treatment within the first 15 days of the first cycle because of skin rash and severe cholangitis. For all 35 enrolled patients, 92.5 and 86.3% of the initially planned dose was administered for gemcitabine and S-1, respectively.

Table 2 Tumor response

	No. of patients	Response rate (%)	Disease control rate (%)
Overall	35	34.3	82.9
Location of primary tumor			
Gallbladder	14	28.6	64.3
Intrahepatic bile duct	14	28.6	92.9
Extrahepatic bile duct	6	50.0	100
Ampulla of Vater	1	100	100

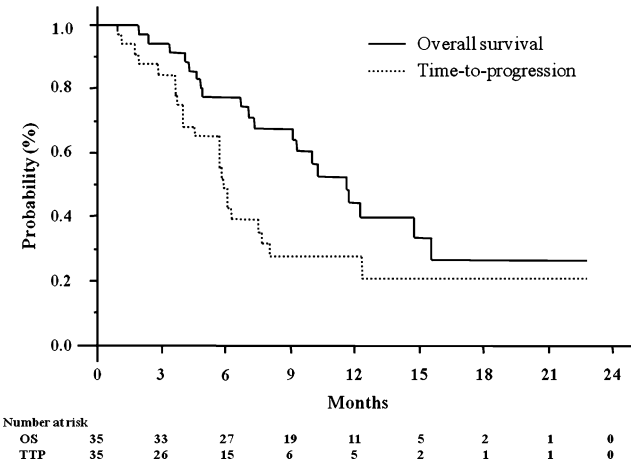

Fig. 1 Time-to-progression (*dashed line*) and overall survival (*solid line*) curves of patients with advanced biliary tract cancer receiving gemcitabine and S-1 combination chemotherapy

The incidence of major adverse events is presented in Table 3. No treatment-related death occurred. Only one patient suspended the study treatment because of drug toxicity (grade 2 skin rash). The major grade 3–4 adverse events were leukopenia (23%), neutropenia (34%) and anemia (20%). The most common non-hematological toxicities were nausea, anorexia, stomatitis and pigmentation. Obstructive jaundice or cholangitis occurred in nine patients (26%) without severe neutropenia.

Biliary events and drainages

Prior to the initiation of the study treatment, 11 patients (31%) required biliary drainage for obstructive jaundice. Of these patients, nine (82%) were drained by internal

Table 3 Toxicity

	Grade 1–2 (%)	Grade 3–4 (%)
Leukopenia	40	23
Neutropenia	26	34
Anemia	66	20
Thrombocytopenia	51	6
Nausea	26	0
Vomiting	9	0
Anorexia	20	3
Stomatitis	23	0
Diarrhea	9	0
Constipation	14	0
Skin rash	17	0
Pigmentation	29	0

biliary stents. After the initiation of the study treatment, nine patients (26%) developed obstructive jaundice or cholangitis, resulting in transient discontinuation of the treatment. Overall, eight of the nine patients (89%) were able to restart the study treatment after the biliary event subsided through biliary interventions.

Discussion

This multicenter, phase II study on gemcitabine combined with S-1 for advanced BTC shows that this regimen has a promising tumor response without an increased risk of severe drug-related adverse events. The anti-tumor effect of this combination chemotherapy is equivalent or superior to those in previous phase II studies (Table 4), but it is difficult to make direct comparisons because of differences in patient characteristics. Moreover, although this study was a phase II study, the median overall survival time of gemcitabine and S-1 combination chemotherapy (11.6 months) was equivalent to that of gemcitabine and cisplatin combination chemotherapy reported from the ABC-02 study (11.7 months) and BT-22 study (11.2 months) [4, 5].

The toxicities of this combination chemotherapy were quite mild. Myelosuppression was the most common toxic effect, although this adverse event was subsequently recovered from without neutropenic fever. The grade 3/4 myelosuppression rate of gemcitabine and S-1 combination chemotherapy (6–34%) was higher than that of gemicitabine and cisplatin combination chemotherapy (6.3–22.6%) reported from ABC-02 study [4]. However, a randomized phase II study (BT-22 study) of gemcitabine and cisplatin combination chemotherapy conducted in Japan reported grade 3/4 myelosuppression rate of 29.3–56.1%, which was extremely different from the ABC-02 study [5]. An advantage of this combination chemotherapy over oxaliplatin and capecitabine is that symptomatic toxicity is less likely to occur. Peripheral sensory neurotoxicity due to oxaliplatin and hand–foot syndrome induced by capecitabine might worsen patient's quality of life. From this point of view, we believe that gemcitabine and S-1 combination chemotherapy is superior to regimens using gemcitabine with oxaliplatin or capecitabine.

Patients with advanced BTC sometimes present with obstructive jaundice or cholangitis, which are obstacles to chemotherapy. Adequate management of these biliary events is crucial to the safe initiation and continuation of chemotherapy. Nevertheless, little information about biliary event is available from previous studies of advanced BTC. In the present study, most of the patients who presented with obstructive jaundice or cholangitis could be started or restarted on chemotherapy after resolution of these biliary events.

Table 4 Combination chemotherapy for advanced biliary tract cancer

Author	Year	Regimen	*N*	RR (%)	Median TTP/PFS (months)	Median OS (months)
Doval [28]	2004	GEM + cisplatin	30	37	4.2	4.7
Thongprasert [29]	2005	GEM + cisplatin	40	28	4.8	8.4
Kim [30]	2006	GEM + cisplatin	29	35	3.0	11.0
Lee [31]	2008	GEM + cisplatin	35	17	3.2	8.6
Furuse [5]	2009	GEM + cisplatin	41	20	5.8	11.2
Valle [4]	2009	GEM + cisplatin	204	26	8.4	11.7
Andre [6]	2004	GEM + oxaliplatin	33	36	5.7	15.4
Harder [7]	2006	GEM + oxaliplatin	31	26	6.5	11.0
Andre [8]	2008	GEM + oxaliplatin	70	15	3.4	8.8
Kim [9]	2009	GEM + oxaliplatin	40	15	4.2	8.5
Knox [10]	2005	GEM + capecitabine	45	31	7.0	14.0
Cho [11]	2005	GEM + capecitabine	44	32	6.0	14.0
Riechelmann [12]	2007	GEM + capecitabine	75	29	6.2	12.7
Kim [32]	2003	Capecitabine + cisplatin	42	21	3.7	9.1
Hong [33]	2007	Capecitabine + cisplatin	32	41	3.5	12.4
Nehls [34]	2008	Capecitabine + oxaliplatin	65	28	NR	NR
Kim [35]	2008	S-1 + cisplatin	51	30	4.8	8.7
Oh [36]	2008	S-1 + oxaliplatin	15	7	1.4	3.1
Present study	2009	GEM + S-1	35	34	5.9	11.6

RR Response rate, *TTP* time to progression, *PFS* progression-free survival, *OS* overall survival, *GEM* gemcitabine, *NR* not reported

Dose modification is recommended when S-1 is administered to Western patients. The conversion rate of tegafur (a component of S-1) to fluorouracil differs in Asians and whites because of polymorphic differences in the CYP2A6 gene [24–26]. Ajani et al. reported phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric cancer and concluded that the recommended dose of S-1 was 50 mg/m^2 per day in the Western population, which is lower than the Japanese recommended dose (80 mg/m^2 per day) [27]. It would be better to adopt the recommended dose of S-1 (50 mg/m^2 per day) when treating Western patients with gemcitabine and S-1 combination chemotherapy for advanced BTC.

In conclusion, gemcitabine and S-1 combination chemotherapy is well tolerated and has a promising efficacy in patients with advanced BTC. A phase III study of gemcitabine and S-1 combination chemotherapy versus gemcitabine and cisplatin combination chemotherapy is needed to identify the best first-line regimen for the treatment of advanced BTC.

Conflict of interest statement None.

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