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ORIGINAL ARTICLE

Phase I trial of oral S-1 combined with gemcitabine and cisplatin for advanced biliary tract cancer (KHBO1002)

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Abstract
Purpose We aimed to determine the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLTs) of the addition of S-1, an oral fluorouracil derivative, to gemcitabine and cisplatin combination therapy, which is the current standard treatment for advanced biliary tract cancer.
Methods Patients with histologically or cytologically confirmed unresectable or recurrent biliary tract cancer were eligible for inclusion. The planned dosages of gemcitabine (mg/m^2)/cisplatin (mg/m^2)/S-1 (mg/m^2/day) were as follows: level 0, 800/25/60; level 1, 1,000/25/60; and levels 2 and 3, 1,000/25/80. In each cycle, gemcitabine and cisplatin were intravenously administered on day 1 (or days 1 and 8 at level 3), and S-1 was orally administered twice daily on days 1–7 (or days 1–14 at level 3); this was repeated every 14 days (or 21 days at level 3).
Results Seventeen patients were enrolled, and level 1 was chosen as the starting dose. Two of six patients developed DLTs (grade 4 neutropenia and grade 3 febrile neutropenia) at level 1, and the dose was escalated to level 2. DLTs (grade 3 rashes and grade 3 vasovagal reactions) occurred in two of six assessable patients at level 2; we then proceeded to level 3. The first three assessable patients enrolled at level 3 developed DLTs (two cases of grade 4 neutropenia, one of grade 4 leucopenia, two of grade 3 fatigue, one of grade 3 anorexia, and one of grade 3 febrile neutropenia) during their first cycle, and this dose was determined to be the MTD. Therefore, we selected level 2 as the recommended dose (RD) for a subsequent phase II study.
Conclusions We determined the RD of gemcitabine/cisplatin/S-1 combination therapy for advanced biliary tract cancer; we are proceeding to a phase II study to investigate the efficacy of this combination therapy for advanced biliary tract cancer.

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

Introduction

Biliary tract cancer is one of the most lethal malignancies worldwide, with surgery representing the only potentially curative treatment for this disease. However, many cases are diagnosed too late for curative resection, and even if surgery can be performed, the likelihood of relapse is very high [6, 12]. Patients with unresectable or recurrent disease have been treated with gemcitabine-based chemotherapy in daily clinical practice [1, 9, 16, 18]. Since the ABC-02 study found that the gemcitabine/cisplatin combination therapy significantly prolonged median survival time (MST) from 8.1 to 11.7 months (hazard ratio, 0.64; $P < 0.001$) over gemcitabine monotherapy [25], gemcitabine/cisplatin combination therapy has become accepted as the standard therapy for advanced biliary tract cancer. Similar results were observed in a randomized phase II study conducted in Japan (BT-22 study) [17].

S-1 is an oral fluoropyrimidine prodrug that has confirmed efficacy against various solid tumors, both alone and in combination with other cytotoxic drugs [5, 8, 11, 13–15, 19, 20]. S-1 monotherapy has yielded good results in chemotherapy-naïve patients with advanced biliary tract cancer [3, 23]. In phase II studies, we and Sasaki et al. have recently demonstrated promising efficacy for gemcitabine/S-1 combination therapy with acceptable toxicity among patients with advanced biliary tract cancer [7, 22].

On the basis of these findings, we expected that the addition of S-1 would produce an additive or synergic increase in the efficacy of gemcitabine/cisplatin combination therapy. However, the efficacy of gemcitabine, cisplatin, and S-1 combination therapy has not been investigated in patients with advanced biliary tract cancer. Therefore, we designed this phase I study to evaluate the safety of the addition of S-1 to gemcitabine/cisplatin combination therapy and to determine the maximum-tolerated dose (MTD) and recommended dose (RD) of this combination therapy in patients with advanced biliary tract cancer.

Patients and methods

Eligibility criteria

Patients with advanced biliary tract cancer that was not amenable to potentially curative surgery or that had recurred after surgery were eligible for inclusion if they met the following criteria: presence of histologically or cytologically confirmed biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer); Eastern Cooperative Oncology Group performance status of 0–1; age ≥20 years; adequate bone marrow function (neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3), liver function (total bilirubin ≤3.0 mg/dL, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] ≤150 IU/L), and renal function (creatinine clearance ≥60 ml/min); and adequate oral intake. All patients provided written informed consent. The exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia; severe heart disease; uncontrollable diabetes mellitus; active infection; pregnancy or lactation; women of childbearing age, unless using effective contraception; severe drug hypersensitivity; mental disorder; watery diarrhea; moderate or marked pleural effusion or ascites; and other serious medical conditions. All procedures were performed in accordance with the 1964 Declaration of Helsinki.

Study design

This dose-escalating phase I study (ClinicalTrials.gov ID NCT01284413; UMIN ID 000004468) was designed by the Kansai Hepatobiliary Oncology Group (KHBO) and was conducted in four institutions in Japan. The protocol was approved by the institutional review board at each institution. Patient registration and data management were conducted at an independent data center at the Osaka Medical

Table 1 Dose and treatment schedule at each level

	Gemcitabine (mg/m^2)	S-1 (mg/body/day)			Cisplatin (mg/m^2)	Administration of gemcitabine and cisplatin	Administration of S-1	Interval
		BSA < 1.25	1.25 < BSA < 1.5	1.5 < BSA				
Level 0	800	60	80	100	25	Day 1	Days 1–7	Every 2 weeks
Level 1	1,000	60	80	100	25	Day 1	Days 1–7	Every 2 weeks
Level 2	1,000	80	100	120	25	Day 1	Days 1–7	Every 2 weeks
Level 3	1,000	80	100	120	25	Days 1, 8	Days 1–14	Every 3 weeks

BSA body surface area

Center for cancer and cardiovascular diseases. All laboratory tests required to assess eligibility were completed within 28 days before the start of protocol treatment. The doses and treatment schedules at each level are summarized in Table 1; these were based on previous studies evaluating gemcitabine/cisplatin or gemcitabine/S-1 for advanced biliary tract cancer [7, 17, 21, 25].

Definition of dose-limiting toxicities (DLTs), maximum-tolerated dose (MTD), and recommended dose (RD)

Dose-limiting toxicities (DLTs) were determined during the first two cycles (or one cycle at level 3). DLT was defined according to the common toxicity criteria adverse events (CTCAE) version 4.0, as one or more of the following events: (1) grade 3–4 neutropenia complicated by fever, (2) grade 4 leucopenia or neutropenia, (3) grade 4 thrombocytopenia or (4) any other grade 3–4 non-hematological toxicity except abnormal blood test results not relevant to study drugs. At least three patients were enrolled at each dose level. If DLT was observed during the first two cycles (or one cycle at level 3) in one or two patients, three additional patients were enrolled at that dose level. If only one or two of the six patients experienced DLT, the dose was escalated to the next level. There was no dose escalation in individual patients. MTD was defined as the dose that produced DLTs in three or more of the six patients or in all three initial patients. If MTD was reached at level 1, which was selected as the starting dose, the dose was de-escalated to level 0. RD was defined as a dose lower than MTD, considering the toxicity and tolerability observed in this study.

Treatment

For all patients, the first course of chemotherapy was conducted at an inpatient clinic to monitor the toxicity closely. Chemotherapy was started and repeated on day 1 if the neutrophil count was $\geq$1,500/mm^3; platelet count was $\geq$100,000/mm^3; total bilirubin was $\leq$3.0 mg/dL; AST/ALT was $\leq$150 IU/l; creatinine was $\leq$1.2 mg/dL; no stomatitis/diarrhea of grade 2 or higher; and no fever (>38°C) due to infection or non-hematological toxicities of grade 3 or higher (except for abnormal blood test results not relevant to study drugs). If the patient did not meet the above criteria, chemotherapy was delayed by 1 week or more until recovery. S-1 was discontinued if the patient was found to meet any of the following criteria during the treatment course: neutrophil count was <1,000/mm^3; platelet count was <75,000/mm^3; total bilirubin was >3.0 mg/dL; AST/ALT was >150 IU/l; stomatitis/diarrhea of grade 2 or higher; fever (>38°C) due to infection or non-hematological toxicities of grade 3 or higher (except for abnormal blood test results not relevant to study drugs). If neutropenia (grade 4), thrombocytopenia (grade 4), febrile neutropenia, or non-hematological toxicity (grade 3) associated with gemcitabine occurred, the subsequent gemcitabine dose was reduced to 800 mg/m^2. If further toxicity occurred with the reduced dose, it was further reduced to 600 mg/m^2. If a further dose reduction was necessary, the subsequent gemcitabine dose was reduced by 20%. If diarrhea, stomatitis, anorexia, nausea, or fatigue (grade 3) associated with S-1 occurred, the dose of S-1 was reduced as follows at the subsequent cycle: 60/50, 80/60, 100/80, or 120/100 mg/day (before/after). No dose re-escalation was allowed. The protocol treatment was continued until any of the following occurred: deterioration of general condition due to disease progression; unacceptable toxicity including non-hematological toxicity of grade 4; a >6-week delay of the schedule as a result of treatment-related toxicity; or patient refusal.

Pretreatment and follow-up evaluation

Pretreatment evaluation included obtaining the patient's medical history and performing a physical examination, imaging test using contrast-enhanced computed tomography or magnetic resonance imaging, blood tests, an electrocardiogram, and chest X-rays. Creatinine clearance was calculated using the Cockcroft–Gault formula. During treatment cycles, physical examinations and blood tests were scheduled on day 1 (and day 8 at level 3). Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were measured at the time patients were enrolled in the study and every month thereafter. Toxicity was evaluated using the CTCAE v4.0. In patients with measurable target lesions, the objective response rate was assessed according to the response evaluation criteria in solid tumors (RECIST) version 1.1 [2], and imaging tests were planned at 12 weeks after the start of treatment. Additional imaging tests were performed if clinically indicated or at the discretion of the treating physician.

Results

Patient characteristics

Seventeen patients, whose characteristics are shown in Table 2, were enrolled between February and August 2011. The median age was 61 years (range, 55–77 years) and no patients had recurrent disease. Eight patients (47%) had intrahepatic bile duct cancer, five had gallbladder cancer (29%), three (18%) had extrahepatic bile duct cancer, and one (6%) had ampullary cancer. Ten patients (58%) required biliary drainage before the start of treatment.

Table 2 Patient characteristics

Sex	
Male	8 (47%)
Female	9 (53%)
Median age (years)	61 (range, 55–77)
Primary lesion	
Intrahepatic	8 (47%)
Extrahepatic	3 (18%)
Gallbladder	5 (29%)
Ampulla of vater	1 (6%)
Disease status	
Unresectable	17 (100%)
Recurrent	0 (0%)
Performance status (0/1)	16/1
Biliary drainage	10 (58%)
Median CEA (ng/ml)	3.4 (range, 1–185)
Median CA19-9 (U/ml)	292 (range, 1–13,700)

CEA carcinoembryonic antigen, *CA* carbohydrate antigen

DLTs

DLTs at each dose level are summarized in Table 3. Level 1 was chosen as the starting dose. Three patients were assigned to level 1; one patient developed DLT, and three additional patients were assigned to this level. In total, two of the six patients at level 1 developed DLTs (grade 4 neutropenia and grade 3 febrile neutropenia), and the dose was escalated to level 2. At dose level 2, DLT was observed in one of the first three patients, and four additional patients were assigned to this level. In total, two of the six assessable patients developed DLTs (grade 3 maculo-papular rash and grade 3 vasovagal reaction), and the dose was further escalated to level 3. At level 3, DLTs were observed in three of the first three assessable patients (grade 4 neutropenia [$n = 1$], grade 3 fatigues [$n = 2$], grade 3 anorexia [$n = 1$], and grade 3 febrile neutropenia [$n = 1$]), and level 3 was determined to be MTD. Two patients (one patient each at levels 2 and 3) were not assessable for DLTs because of early treatment withdrawal due to obstructive jaundice related to the primary disease.

Toxicity

Common hematological and non-hematological adverse events observed during the first two cycles of chemotherapy (or one cycle for level 3) are listed in Tables 4 and 5, respectively. Grade 3–4 neutropenia, leucopenia, thrombocytopenia, and anemia were observed in 29, 24, 18, and 6% of the patients, respectively. Febrile neutropenia occurred in one patient each at level 1 and 3. Common non-hematological adverse events included the following: anorexia (71%), nausea (53%), fatigue (41%), vomiting (24%), and elevation of AST (59%) and ALT (71%). Furthermore, hyperbilirubinemia (35%) was common; however, this was mostly associated with the obstruction of the biliary tract caused by the primary disease. Among these adverse events, the proportion of grade 3–4 adverse events was generally low (Table 5). Based on the incidence of DLTs and adverse events, we selected level 2 as RD for a phase II study to evaluate the efficacy of this combination therapy.

Efficacy

Although assessment of tumor response was not the primary objective of this study, imaging test to evaluate tumor response was planned 12 weeks after the start of treatment. Of seventeen patients, nine were evaluable for response by RECIST, two showed partial response (one each at dose level 1 and 2), six had stable disease (four at dose level 1 and 2 at dose level 2), and one patient (at dose level 1) showed disease progression, giving an overall response rate of 22%.

Discussion

The primary aim of this study was to determine MTD and RD of gemcitabine/cisplatin/S-1 combination therapy for advanced biliary tract cancer. We observed that dose level 3 represented MTD and dose level 2 was defined as RD.

We anticipated that the addition of S-1 would increase the efficacy of gemcitabine/cisplatin combination therapy because our previous multi-institution phase II study demonstrated promising efficacy of the addition of S-1 to gemcitabine, resulting in an MST of 12.7 months and 1-year survival rate of 52% [7]. Moreover, Sasaki et al. [21] conducted a phase II study of gemcitabine/S-1 and reported similar efficacy, with an MST of 11.6 months and 1-year survival rate of 44%. The combination of S-1 and cisplatin was reported to have high response rate with tolerable toxicity in patients with solid tumors including biliary tract cancer [5, 10, 11]. A randomized phase III study demonstrated the superiority of S-1/cisplatin combination therapy to S-1 monotherapy in patients with gastric cancer in Japan [11]. In addition, preclinical studies, in which the addition of S-1 to gemcitabine or cisplatin demonstrated synergistic or additive effects in vitro [26], also support the concept of the addition of S-1 to gemcitabine/cisplatin combination therapy. An absence of cross-resistance between S-1 and gemcitabine was indirectly suggested by the fact that S-1 has modest activity in patients with biliary tract cancer refractory to gemcitabine [22].

However, we considered the possibility that the addition of S-1 to gemcitabine/cisplatin combination therapy may increase the incidence of severe adverse events, making

Table 3 Dose-limiting toxicities at each level

Patient no.	Level	Age (year)	Sex	Tumor type	PS	Blood test results at baseline					DLTs	Biliary drainage	Response by RECIST
						WBC (/mm^3)	Neu (/mm^3)	PLT ($\times 10^4$/mm^3)	Cre (mg/dL)	T-Bil (mg/dL)			
1	1	61	Male	Intrahepatic	0	13,000	9,698	37.5	0.9	1.8	None	Yes	PD
2	1	59	Male	Intrahepatic	0	8,350	5,185	24.6	0.7	1.5	None	No	PR
3	1	65	Female	Intrahepatic	0	8,200	5,400	23.7	0.5	2.6	Gr 4 neutropenia	Yes	SD
4	1	63	Female	Intrahepatic	0	4,980	3,984	11.5	0.5	1.7	Gr 3 febrile neutropenia	Yes	SD
5	1	76	Female	Intrahepatic	0	5,760	3,813	28.2	0.8	0.4	None	No	SD
6	1	62	Male	Intrahepatic	0	6,700	5,200	31.6	0.7	0.8	None	Yes	SD
7	2	72	Male	Extrahepatic	0	8,510	5,685	19.9	0.6	0.9	Gr 3 maculopapular rash	Yes	NE
8	2	60	Male	Intrahepatic	0	15,010	11,633	26.5	0.9	0.7	None	No	SD
9	2	72	Female	Gallbladder	0	4,400	2,500	35.7	0.6	1.7	None	Yes	PR
10	2	55	Female	Gallbladder	1	6,900	4,168	32.6	0.7	0.6	None	Yes	NE
11	2	77	Male	Gallbladder	0	8,170	5,882	21.3	0.8	0.5	None	No	SD
12	2	69	Female	Gallbladder	0	8,000	6,000	27.5	0.5	0.5	NE	No	NE
13	2	75	Male	Extrahepatic	0	6,600	4,626	22.8	1	0.2	Gr 3 vasovagal reaction	Yes	NE
14	3	57	Female	Gallbladder	0	4,400	4,000	15.2	0.5	0.6	Gr 3 fatigue	No	NE
15	3	56	Female	Ampullary	0	4,330	2,620	22.6	0.5	0.7	NE	Yes	NE
16	3	56	Female	Intrahepatic	0	4,300	2,700	22.9	0.5	0.6	Gr 4 neutropenia	No	NE
17	3	72	Male	Extrahepatic	0	2,900	1,700	20.9	0.7	0.6	Gr 3 fatigue, anorexia, and febrile neutropenia	Yes	NE

DLT dose-limiting toxicity, *Gr* grade, *NE* not evaluable, *Neu* neutrophil, *PD* disease progression, *PLT* platelet, *Cre* creatinine, *T-Bil* total bilirubin, *PR* partial response, *SD* stable disease, *WBC* white blood cell

Table 4 Hematological adverse events during the first two cycles (or one cycle at level 3)

	Level 1 ($n = 6$)		Level 2 ($n = 7$)		Level 3 ($n = 4$)	
	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4
Neutropenia	0	3	2	0	1	2
Leucopenia	0	3	2	0	2	1
Thrombocytopenia	1	1	2	0	2	1
Anemia	4	0	2	1	1	0
Febrile neutropenia	N/A	1	N/A	0	N/A	1

N/A not applicable

Table 5 Non-hematological adverse events during the first two cycles (or one cycle at level 3)

	Level 1 ($n = 6$)		Level 2 ($n = 7$)		Level 3 ($n = 4$)	
	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4
Anorexia	4	0	3	1	3	1
Nausea	2	0	3	1	3	0
Vomiting	2	0	1	0	1	0
Fatigue	3	0	2	0	0	2
Diarrhea	1	0	0	0	0	0
Stomatitis	1	0	0	0	1	0
Constipation	1	0	1	0	1	0
Rash	0	0	0	1	0	0
Fever	1	0	0	0	0	0
Vasovagal reaction	0	0	0	1	0	0
Infections (others)	2	0	0	0	0	0
Biliary tract infection	N/A	0	N/A	0	N/A	0
AST	5	0	2	1	2	0
ALT	6	0	2	1	2	1
Hyperbilirubinemia	3	0	1	1	1	0
Creatinine	1	0	0	0	0	0

N/A not applicable

this treatment unacceptable for patients with advanced biliary tract cancer and negating the benefit of increased efficacy. Therefore, we started with a biweekly schedule while keeping the dose at each administration identical to that in the standard therapy (1,000 mg/m^2 for gemcitabine and 25 mg/m^2 for cisplatin). At levels 1 and 2, DLTs occurred in two out of six assessable patients, and the dose was escalated to level 3, which was the highest level predefined in our protocol and was determined to be the MTD. Grade 3 or higher toxicities observed at levels 1 and 2 included neutropenia (23%), leucopenia (23%), thrombocytopenia (8%), anemia (8%), febrile neutropenia (8%), anorexia (8%), and nausea (8%), which were well comparable to those reported in previous studies using gemcitabine/cisplatin or gemcitabine/S-1 [7, 17, 21, 25]. Consequently, we selected level 2 as RD for a subsequent phase II study. Level 2 consisted of intravenous administration of gemcitabine (1,000 mg/m^2) and cisplatin (25 mg/m^2) on day 1 and oral administration of S-1 (80 mg/m^2) on days 1–7 every 2 weeks. The dose intensity of gemcitabine and S-1 was equivalent to that of the therapy employed by Sasaki et al., which consisted of intravenous administration of gemcitabine (1,000 mg/m^2) on days 1 and 15 and oral administration of S-1 (80 mg/m^2) on days 1–14 every 4 weeks and still demonstrated promising efficacy [21]. From a different view point, we can safely add cisplatin to gemcitabine and S-1 combination therapy without reducing the dose intensity of these two drugs.

The first course of chemotherapy was conducted at an inpatient clinic for all patients, but the toxicity was readily manageable, and subsequent cycles were performed at an outpatient clinic. Recently, Gruenberger et al. [4] reported the prolonged survival of patients with advanced biliary tract cancer who underwent potentially curative secondary resection after a major response to a therapy consisting of three anticancer drugs (gemcitabine/oxaliplatin/cetuximab). We expect that some patients experience a similar response to the combination therapy tested in our study and undergo potentially curative secondary surgery. Furthermore, a recent success of FOLFIRINOX therapy, which consisted of three cytotoxic drugs (5-fluorouracil/oxaliplatin/irinotecan) and demonstrated a significant survival

advantage over gemcitabine monotherapy in patients with pancreatic cancer [24], also supports the concept of our therapy.

In summary, we determined RD of gemcitabine/cisplatin/S-1 combination therapy with comparable toxicity to the standard therapy of gemcitabine/cisplatin for the treatment of advanced biliary tract cancer. To the best of our knowledge, this is the first study to investigate the safety and tolerability of gemcitabine/cisplatin/S-1 combination therapy for advanced biliary tract cancer. We are now proceeding to a phase II study to investigate the efficacy of this combination therapy for advanced biliary tract cancer.

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