Original Article

A multi-institution phase II study of gemcitabine/cisplatin/S-1 (GCS) combination chemotherapy for patients with advanced biliary tract cancer (KHBO 1002)

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Abstract

Purpose: Gemcitabine/cisplatin combination therapy has been the standard palliative chemotherapy for patients with advanced biliary tract cancer (BTC). We aimed to evaluate the efficacy and safety of adding S-1 to gemcitabine/cisplatin combination therapy for patients with advanced BTC.

Methods: Patients with histologically or cytologically confirmed unresectable or recurrent BTC were eligible for inclusion. The primary endpoint was overall survival. Based on the results of our preceding phase I study, gemcitabine and cisplatin were administered intravenously at doses of 1,000 mg/m^2 or 25 mg/m^2, respectively, on day 1, and oral S-1 was administered daily at a dose of 80 mg/m^2 on days 1–7 every 2 weeks. This study was registered with ClinicalTrials.gov (NCT01284413) and the UMIN Clinical Trials Registry (ID 000004468).

Results: Fifty patients enrolled between October 2011 and August 2012 were evaluated. After a median follow-up of 15.1 months (range, 2.4–24.4 months), the median overall survival time was 16.2 months [95% confidence interval (CI), 10.2–22.2 months], and the 1-year overall survival rate was 59.9% (95% CI, 46.2–73.5%). The grade 3−4 hematological toxicities were as follows: neutropenia (32%), anemia (32%), thrombocytopenia (10%), and febrile neutropenia (4%)**.** The common grade 3−4 non-hematological toxicities were biliary tract infection (14%), anorexia/nausea (10%) and fatigue (8%).

Conclusions: Gemcitabine/cisplatin/S-1 combination chemotherapy offered a promising survival benefit with manageable toxicity in patients with advanced BTC. A randomized phase III trial to investigate the

efficacy of this regimen compared to gemcitabine/cisplatin combination therapy in patients with advanced BTC is now underway (UMIN000014371/NCT02182778).

Keywords: Biliary – Gemcitabine – Cisplatin – S-1 – Chemotherapy

Running title: GEM/CDDP/S-1 therapy for advanced BTC

Introduction

Biliary tract cancer (BTC) is one of the most lethal malignancies worldwide, and surgery represents 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, there is a significant likelihood of relapse [1]. Patients with unresectable or recurrent disease have been treated with systemic chemotherapy if they are considered to be good candidates [2,3]. After the ABC-02 study found that the gemcitabine/cisplatin combination therapy significantly prolonged the median survival time (MST) from 8.1 to 11.7 months (hazard ratio, 0.64; $P < 0.001$) compared to gemcitabine monotherapy, this combination therapy became the standard treatment for advanced BTC [4]. Similar results were observed in a randomized phase II study conducted in Japan (BT-22 study), which reported MSTs of 11.2 and 7.7 months for the months for the gemcitabine/cisplatin and gemcitabine monotherapy arms, respectively [5].

S-1 is an oral fluoropyrimidine prodrug that has confirmed efficacy against various solid tumors both alone and in combination with other cytotoxic drugs [6-14]. S-1 monotherapy has yielded good results in patients with advanced BTC [7,8,14]. In combination with gemcitabine, S-1 has also demonstrated promising MSTs, ranging from 11.6 to 12.7 months [10,12,13].

On the basis of these findings, we expected that the addition of S-1 would produce an additive or synergistic increase in the efficacy of gemcitabine/cisplatin combination therapy, which is now the global

standard regimen. We have previously determined the recommended dose (RD) of gemcitabine/cisplatin/S-1 (GCS) combination therapy for patients with advanced BTC in the preceding phase I study [15]. In this multi-institution phase II study, we aimed to evaluate the efficacy of this combination therapy.

Patients and methods

Eligibility criteria

Patients with advanced BTC who were not amenable to potentially curative surgery (unresectability was determined at the discretion of each institution) or who had experienced recurrence after surgery were eligible for inclusion if they met the following criteria: presence of histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma of the biliary tract (intra- or extra-hepatic cholangiocarcinoma, gallbladder cancer, or ampulla of Vater cancer); Eastern Cooperative Oncology Group performance status of 0–1; age ≥ 20 years; no prior chemotherapy or radiotherapy except for adjuvant chemotherapy, which had been completed at least 6 months before enrolment; adequate bone marrow (neutrophil count ≥ 1,500/mm^3, platelet count ≥ 100,000/mm^3), liver [total bilirubin ≤ 3.0 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT)] ≤ 150 IU/L], and renal functions (calculated creatinine clearance using Cockcroft and Gault formula ≥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; age within the childbearing range for women, unless effective contraception was being used; severe drug hypersensitivity; mental disorder; watery diarrhoea; moderate or marked pleural effusion or ascites necessitating drainage; and other serious medical conditions.

Study design

This phase II study (ClinicalTrials.gov ID NCT01284413; UMIN ID 000004468) was designed by the Kansai Hepatobiliary Oncology Group (KHBO) and was conducted in 11 Japanese institutions. The protocol was approved by the institutional review board at each institution, and patient registration and data management were conducted at a data center at the Osaka Medical Center for Cancer and Cardiovascular Diseases.

Treatment

Gemcitabine/cisplatin was infused at a dose of 1000/25 mg/m^2 over 30/60 min on day 1. S-1 was administered orally twice a day for 7 consecutive days. Doses of S-1 were calculated 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. Chemotherapy was started and repeated on day 1 if the neutrophil count was $\geq$ 1,500/mm^3, the platelet count was $\geq$ 100,000/mm^3, the total bilirubin was $\leq$ 3.0 mg/dL, the AST/ALT was $\leq$ 150 IU/L, the creatinine was $\leq$ 1.2 mg/dL, there was no stomatitis/diarrhea of grade 2 or higher,

and there was 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: the neutrophil count was < 1,000/mm^3, the platelet count was < 75,000/mm^3, the total bilirubin was > 3.0 mg/dL, the AST/ALT was > 150 IU/L, stomatitis/diarrhea of grade 2 or higher, or the patient had a 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 at the subsequent cycle as follows: 80/60, 100/80, or 120/100 mg/day (before/after). If still further reduction of S-1 was necessary, patients were withdrawn from the study. Cisplatin was suspended until recovery if the patient was found to meet any of the following criteria during the treatment course: neuropathy (grade 2 or higher) or hearing disturbance associated with cisplatin. 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 or repeated treatment-related

toxicity, a >6-week delay of the schedule as a result of treatment-related toxicity, patient refusal, or tumor response allowing potential curative resection.

Pre-treatment and follow-up evaluation

Pre-treatment evaluation included obtaining the patient's medical history and performing a physical examination, imaging tests using contrast-enhanced computed tomography or magnetic resonance imaging, blood tests, an electrocardiogram and chest X-rays. Physical examinations and blood tests were scheduled on day 1 of each course. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were measured at the time of enrolment in the study and once monthly thereafter. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events 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 [16], and imaging tests were planned for 12 weeks after the initiation of treatment. Additional imaging tests were performed if clinically indicated or at the discretion of the treating physician.

Statistical analysis

The primary endpoint was overall survival. The secondary endpoints were safety and response rate. A sample size of 50 patients was determined to reject a null hypothesis of a MST of 11 months and accept an alternative hypothesis of a MST of 16 months, with a one-sided significance level of 0.05 and a power

of 80%, assuming 3-years of recruitment and an additional 2 years of follow-up. We could finish enrolling patients earlier than initially planned (11 months) and this analysis was conducted 16 months after the enrollment of the last patient (November 2013). Overall survival was defined as the time from the date of registration to death from any cause. Progression-free survival (PFS) was defined as the time from the date of registration to tumor progression or death from any cause. Patients who were not dead or did not have disease progression at the time of this analysis were censored at the date of their last follow-up. Overall survival and PFS were analyzed using the Kaplan–Meier method. The IBM SPSS version 22 software program (IBM, Chicago, IL) was used for all statistical analyses.

Results

Patient characteristics

Fifty-one patients were enrolled between October 2011 and August 2012 at 11 institutions in Japan. One patient dropped out before protocol treatment due to disease progression and 50 patients were evaluable for survival and safety. The patient characteristics are summarized in Table 1. The median age was 68 years (range 33–83 years). Nineteen patients (38%) had intrahepatic bile duct cancer, 15 (30%) had gallbladder cancer, 12 (24%) had extrahepatic bile duct cancer, and 4 (8%) had ampulla of Vater cancer. Eighteen patients (36%) had undergone biliary drainage before the initiation of chemotherapy. Twelve patients (24%) experienced recurrent disease after undergoing curative surgery and 1 patient had a history of adjuvant chemotherapy. Among 38 patients with unresectable disease, 28 had metastatic disease and 10 had locally advanced disease. Seventeen patients (34%) had no measurable target lesions at baseline, including those with locally advanced disease (n = 10); metastatic lesions which did not meet the RECIST criteria (n = 5); and local recurrence (n = 2) (Supplement 1).

Efficacy

At the time of this analysis (November 2013), 30 patients had died, 16 patients were alive after the discontinuation of protocol treatment, 3 patients were continuing protocol treatment and one patient was lost to follow-up. After a median follow-up of 15.1 months (range, 2.4−24.4 months), the median overall survival time was 16.2 months [95% confidence interval (CI), 10.2–22.2 months], and the 1-year overall

survival rate was 59.9% (95% CI, 46.2%–73.5%) (Figure 1). Of the 33 patients with measurable target regions by RECIST, 8 patients (24%) experienced a partial response (95% CI, 11%−42%), 15 patients (45%) had stable disease, 7 patients (21%) had progressive disease, and 3 patients (9%) were not evaluated.

Toxicity

In total, 514 cycles of GCS combination chemotherapy were delivered, with a median of 7 cycles per patient (range 1–36 cycles; Table 1). The incidences of hematological and non-hematological adverse events are summarized in Tables 2 and 3, respectively. The grade 3–4 hematological toxicities included neutropenia (32%), anaemia (32%), thrombocytopenia (10%) and febrile neutropenia (4%). The grade 4 non-hematological toxicities were biliary tract infection (n = 1), other infection (n = 1), and hepatic hemorrhage (n = 1). Other common grade 3 toxicities were anorexia/nausea (10%), increased ALT/AST (10%/8%), and fatigue (8%).

Post-study treatment

Thirty-two patients (64.0%) received post-study treatment including chemotherapy (n = 26), chemoradiotherapy (n = 3), potentially curative secondary resection after tumor downstaging following chemotherapy (n = 2), and radiotherapy (n = 1). Because other anti-cancer drugs such as oxaliplatin or capecitabine are not approved for BTC in Japan, the regimen of second-line chemotherapy consisted of

the same drugs as those administered during the study period [S-1 monotherapy (n = 8), gemcitabine/cisplatin (n = 7), gemcitabine/S-1 (n = 6), and gemcitabine monotherapy (n = 5)].

Discussion

In our preceding phase I study, we determined the RD of GCS combination therapy, which 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 [15]. The dose intensity of gemcitabine and S-1 in this combination regimen is equivalent to that of the gemcitabine/S-1 combination therapy employed by Sasaki et al., which consisted 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 [10]. Thus, by adopting a biweekly schedule, our combination regimen retains the dose intensity of gemcitabine/S-1 in spite of adding cisplatin.

In this study, we aimed to evaluate the efficacy of the GCS regimen. After a median follow-up of 15.1 months (range, 2.4−24.4 months), MST was 16.2 months (95% CI, 10.2–22.2 months), which met our primary endpoint. One patient was lost to follow-up and censored at a time of less than 1 year following registration. Even if we assume that this patient was dead at the censored time, MST was still 15.3 months (95% CI, 9.8–20.8 months). PFS, which was not included in our predefined endpoints, was estimated to be 9.0 months (95% CI, 5.8–12.0 months). Because patients were not required to have measurable target

lesions in this study, the proportion of patients without measurable target lesions at baseline was relatively high (34%). Similarly, the ABC-02 study also did not require measurable target lesions at study entry and tumor response was not evaluable in 107 patients (26%). We speculated that the increase in patients without measurable target lesions was partly attributable to the advances in diagnostic tests such as positron emission tomography or endoscopic procedures, which enabled physicians to find small metastatic lesions or to select the patients with unresectable locally advanced disease at preoperative examination [17-19]. Because these patients were likely to have a lower tumor burden, which could have a favorable impact on the outcome of chemotherapeutic treatment of advanced BTC, the higher proportion of patients without measurable target lesions could have contributed to the positive MST of the current study. However, even if we excluded these patients (n = 17) from the overall survival analysis, MST was still 15.3 months (95% CI, 7.3–23.3 months). Exclusion of patients with PS ≥ 2 or marked pleural effusion/ascites necessitating drainage also may have affected the current good results. The proportion of patients with other putative prognostic factors such as gall bladder cancer [3,5,20] or recurrent disease [5,21] was 30% and 24%, respectively, which were comparable with those in the ABC-02 study (36% and 21%, respectively) and the BT-22 study (39% and 25%, respectively). Moreover, the patient characteristics in this study did not greatly differ from those of 403 consecutive patients with BTC who received palliative chemotherapy between April 2006 and March 2009 in 18 Japanese institutions [21] (Supplement 2). This suggests that our study cohort represented the patients with BTC

who receive chemotherapy in daily clinical practice rather than selected patients with favorable characteristics.

Our current results were classified into the most favorable outcomes reported in single-arm phase II trials, although cross-study comparisons have limitations. To the best of our knowledge, only 3 previous phase II trials have reported an MST over 15 months for patients with advanced BTC following chemotherapy (Table 4) [22-24]. Our results are line with the previous study by Yamashita et al., which reported an MST of 18.8 months in 21 patients with advanced BTC using a combination of gemcitabine/cisplatin/5-fluorouracil (5 -FU) [24]. Because S-1 is an oral 5-FU drug, adding 5-FU to gemcitabine/cisplatin combination therapy may confer synergic effects and prolong overall survival. Another advantage of adding S-1 to the gemcitabine/cisplatin combination therapy as the first-line therapy is that patients never miss the chance of receiving S-1 during the treatment course. In contrast, implementing a sequential strategy of S-1 administration after the treatment failure of gemcitabine/cisplatin does not always allow the patients to receive this agent due to the aggressive clinical course. For example, less than half of patients (46%) reportedly received S-1 as a second-line chemotherapy following gemcitabine/cisplatin combination therapy [5].

The overall toxicity was generally manageable despite the administration of 3 cytotoxic drugs. We consider that the biweekly schedule largely contributed to the safety of this regimen, and patients

generally continued this treatment in an outpatient setting. The incidence of grade 3−4 neutropenia was comparable to those of previous clinical trials testing gemcitabine plus S-1 or gemcitabine plus cisplatin (Table 5). However, physicians should be cautious regarding the grade 3−4 biliary tract infections, which were observed in 14% of patients. The incidence of grade 3−4 anemia was also high (32%), but we speculate that this was partly attributable to pre-existing anemia, as we did not include hemoglobin levels in the eligibility criteria. Notably, the incidence of diarrhea, which is one of the common adverse events following the administration of S-1, was low (12%) and there was no grade 3−4 diarrhea in this study. We suppose that the biweekly schedule contributed to the reduction of diarrhea associated with S-1. Supporting this idea, Komiyama et al. also reported that there was no grade 3−4 diarrhea in 34 patients with non-small cell lung cancer treated with a biweekly combination of S-1 plus docetaxel [25].

In summary, GCS combination chemotherapy yielded a promising survival benefit with acceptable toxicity in patients with advanced BTC. We have now launched a randomized phase III trial to investigate the efficacy of this regimen compared to gemcitabine/cisplatin combination therapy in patients with advanced BTC (UMIN000014371/NCT02182778).

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Conflict of interest

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None

Figure 1. Overall survival of patients with advanced biliary tract cancer receiving gemcitabine/cisplatin/S-1 combination therapy (n = 50)

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Table 1. Patient Characteristics (n=50)

Gender	
Male	29 (58%)
Female	21 (42%)
Median age (years)	68 (range 33–83)
Primary lesion	
Intrahepatic	19 (38%)
Gall bladder	15 (30%)
Extrahepatic	12 (24%)
Papilla Vater	4 (8%)
Disease status	
Unresectable disease	38 (76%)
Metastatic	28
Locally advanced	10
Recurrent disease	12 (24%)
Measurable target lesion	
Liver	15
Lymph node	13
Primary	12
Peritoneum	2
Lung	2
Spleen	1
None	17
Performance Status (0/1)	34/16
Biliary drainage	18 (34%)

Median no. treatment cycles	7 (range 1–36)
Median CEA (ng/mL)	3.6 (range 1–181)
Median CA19-9 (U/mL)	202 (range 1–>100,000)

CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen.

Table 2. Hematologic adverse events (n = 50)

	Grade 1−2	Grade 3	Grade 4	Incidence of grade 3−4 events (%)
Neutropenia	19	12	4	32%
Leukopenia	31	7	1	16%
Anemia	32	14	2	32%
Thrombocytopenia	28	4	1	10%
Febrile neutropenia	–	2	0	4%

Table 3. Non-hematological adverse events (n = 50)

	Grade 1−2	Grade 3	Grade 4	Incidence of grade 3−4 events (%)
Infection (biliary tract)	−	6	1	14%
Infection (others)	11	2	1	6%
Anorexia/Nausea	38	5	0	10%
Fatigue	31	4	0	8%
Stomatitis	14	1	0	2%
Abdominal pain	7	1	0	2%
Alopecia	13	0	0	0
Pain	11	0	0	0
Vomiting	7	0	0	0
Diarrhea	6	0	0	0
Rash	3	0	0	0
ALT increased	20	5	0	10%
AST increased	25	4	0	8%
Hyperbilirubinemia	20	1	0	2%
Hypoalbuminemia	37	0	0	0
Alkaline phosphatase increased	29	0	0	0
Creatinine increased	6	0	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 4. Comparison of phase II trials reporting MST over 15 months

	Present study	Yamashita et al. [24]	Andre et al. [22]	Gruenberger et al. [23]
Regimen	GEM 1000 mg/m^2 day1 CDDP 25 mg/m^2 day1 S-1 80 mg/m^2 day1-7 Repeated every 2 weeks	GEM 1000 mg/m^2 day1, 8, 15 CDDP 3 mg/m^2 5-FU 150 mg/m^2 day1−5, 8−12, 15−19 Repeated every 4 weeks	GEM*[1] 1000 mg/m^2 day1 Oxaliplatin 100 mg/m^2 day2 Repeated every 2 weeks	GEM*[1] 1000 mg/m^2 day1 Cetuximab 500 mg/m^2 day1 Oxaliplatin 100 mg/m^2 day2 Repeated every 2 weeks
MST (months)	16.2	18.8	15.4	15.2
PFS (months)	9.0	13.4	5.7	8.8
1-year survival rate	59%	58%	57%	NA
Proportion of gall bladder cancer	30%	33%	33%	10%
median CA 19-9 (Range)	202 U/mL (1−100,000)	NA	NA	42 U/mL (9−116)[*2]
Sample size	50	21	33	30

GEM; gemcitabine. CDDP: cisplatin. NA; not available. *1 GEM was infused over 100-min. *2 Interquartile range.

Table 5. Comparison of toxicities in phase II trials testing gemcitabine plus cisplatin or S-1

	Present study	Kanai et al. [12]	Morizane et al. [13]	Sasaki et al. [10]	Okusaka et al. [5]
GEM (mg/m^2)	1000, day 1	1000, day 1, 8	1000, day 1, 8	1000, day 1, 15	1000, day 1, 8
CDDP (mg/m^2)	25, day 1	−	−	−	25, day 1, 8
S-1 (mg/m^2)	80, day 1−7	60, day 1−14	60, day 1−14	80, day 1−14	−
Cycle	2 weeks	3 weeks	3 weeks	4 weeks	3 weeks
Grade 3/4 neutropenia	32%	56%	61%	34%	56%
Grade 3/4 anemia	32%	8%	12%	20%	28%
Grade 3/4 thrombocytopenia	10%	4%	12%	6%	39%
Febrile neutropenia	4%	0%	2%	NA	NA
Grade 3/4 diarrhea	0%	4%	2%	0%	2%
Sample size	50	21	51	33	41

GEM; gemcitabine. CDDP: cisplatin. NA; not available

Supplement 1.

	Unresectable disease (n = 38)		Recurrent disease (n = 12)	
	Distant metastasis (n = 28)	Locally advanced (n = 10)	Distant metastasis (n = 6)	Local recurrence (n = 6)
Measurable targets (Yes/No)	24/4	0/10	5/1	4/2

Supplement 2.

	Current study	Ikezawa et al.
Gender		
Male	29 (58%)	227 (56.3%)
Female	21 (42%)	176 (43.7%)
Median age (years)	68 (range 33–83)	68 (range 30–84)
Primary lesion		
Intrahepatic	19 (38%)	88 (22%)
Gall bladder	15 (30%)	115 (29%)
Extrahepatic	12 (24%)	177 (44%)
Papilla Vater	4 (8%)	23 (6%)
Disease Status		
Unresectable disease	38 (76%)	211 (52%)
Recurrent disease	12 (24%)	192 (48%)
Performance Status (0/1/2)	34/16 (68%/32%)	279/105/19 (69%/26%/5%)
Biliary drainage	19 (38%)	169 (42%)
Median CEA (ng/mL)	3.6 (range 1–181)	3.2 (range 0–2901)
Median CA19-9 (U/mL)	202 (range 1–>100,000)	122 (range 0–>100,000)