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ORIGINAL ARTICLE

Phase II study of gemcitabine and S-1 combination chemotherapy in patients with metastatic biliary tract cancer

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Abstract
Purpose A phase II study was conducted to evaluate the efficacy and safety of gemcitabine and S-1 combination chemotherapy in patients with metastatic biliary tract cancer (BTC).
Methods Patients with pathologically confirmed, unresectable, recurrent, or metastatic adenocarcinoma that originated from the intrahepatic or extrahepatic biliary ducts or gallbladder were assessed for eligibility. The primary end point was the overall response rate (ORR). The treatment consisted of 1,000 mg/m^2 intravenous gemcitabine administered over 30 min on days 1 and 8, and 80 mg/m^2 oral S-1 on days 1–14 of each cycle. The treatment was repeated every 3 weeks.
Results Thirty-eight patients were enrolled between November 2005 and 2010. All patients had metastatic disease, and the primary sites of cancer were as follows: gallbladder in 12 (31.6 %), intrahepatic and extrahepatic bile ducts in 23 (60.5 %), and the ampulla of Vater in 3 (7.9 %) patients. One patient achieved a complete response, and six experienced a partial response. The ORR was 20.6 % (95 % CI 8.5–36.7] in the per-protocol (PP) population, and 18.4 % (95 %CI 6.1–30.7) in the intention-to-treat (ITT) population; the median response duration was 10.8 months. Nineteen patients had stable disease, and the disease control rate was 76.5 % (95 %CI 60.6–87.6) in the PP population. The median progression-free survival was 4.4 months (95 %CI 1.8–6.9), and the median overall survival was 9.0 months (95 %CI 4.0–13.9) with a 1-year survival rate of 44.7 % (95 %CI 29.0–61.5) in the ITT population. Grade 3/4 hematologic toxicities, neutropenia, anemia, and thrombocytopenia were observed in 13 (37.1 %), 9 (25.7 %), 2 (5.7 %), and 2 (5.7 %) patients, respectively. One patient experienced a grade 3 febrile neutropenia without any documented infection. The grade 3/4 non-hematologic toxicities were hepatic toxicity (11.4 %), anorexia (2.9 %), and renal toxicity (2.9 %).
Conclusion Gemcitabine and S-1 combination chemotherapy showed acceptable efficacy and favorable toxicity profiles. Therefore, it might offer an alternative therapeutic strategy in patients with BTC.

Keywords Gemcitabine · S-1 · Biliary tract cancer · Combination chemotherapy · Phase II study

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Introduction

Biliary tract cancer (BTC) is an invasive carcinoma that originates from the epithelial lining of the gallbladder and bile ducts. BTC includes cholangiocarcinoma (intrahepatic,

perihilar, and distal biliary-tree tumors) and carcinoma arising from the gallbladder [1]. Surgical resection of the primary tumor is potentially curative for BTC, but <25 % of patients are eligible for resection at presentation [2]. Systemic chemotherapy is the principal treatment method for patients with unresectable or metastatic BTC [3].

Gemcitabine is a promising agent that has shown efficacy in biliary tract cancer and yields response rates of 8–36 % in BTC when used as a single agent [4]. In phase II trials with patients in advanced BTC, gemcitabine in combination with capecitabine or platinum analogs produced overall response rates (ORRs) of 26–50 % [4]. The ABC-02 study reported a significant survival advantage for gemcitabine and cisplatin (GC) compared with gemcitabine alone in patients with advanced BTC [median overall survival (OS) 11.7 vs. 8.1 months, respectively; $P < 0.001$] [5]. The oral anticancer drug S-1 consists of the 5-FU prodrug tegafur with two biochemical modulators: 5-chloro-2,4-dihydroxypyridine and potassium oxonate [6]. S-1 monotherapy is active against advanced BTC, with ORRs of 21–35 % [7, 8]. In addition, phase II trials of S-1 in combination with gemcitabine reported ORRs of 20–36 % [9–12]. Differences between trials regarding the doses and administration schedules of gemcitabine and S-1 (GS) might explain the ranges of efficacy, dose intensity, and toxicity observed. Therefore, we conducted a phase II study to evaluate a GS combination as the first-line chemotherapy for patients with advanced BTC.

Patients and methods

Eligibility

Patients with pathologically confirmed, unresectable, recurrent, or metastatic adenocarcinoma arising from the intrahepatic or extrahepatic biliary ducts or gallbladder were assessed for inclusion in the current study. All patients had measureable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 [13]. All individuals were aged ≥18 years and met the minimal criteria for the following: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, adequate bone marrow function (defined as a leukocyte count ≥4,000/μL, an absolute neutrophil count ≥1,500/μL, a platelet count ≥100,000/μL, and a serum hemoglobin ≥9 g/dL), renal function (serum creatinine <1.5 mg/dL or creatinine clearance >60 mL/min), and hepatic function (bilirubin level <2.0 mg/dL or AST/ALT levels <2.5-fold the reference values). Prior radiotherapy was permitted if it was not administered to the target lesions selected for this study and had been completed at least 4 weeks prior to study entry.

Patients with recurrence after adjuvant S-1 or gemcitabine-based chemotherapy were not eligible for inclusion, regardless of the time to recurrence. Patients with brain metastasis, obvious bowel obstruction, serous gastrointestinal bleeding, or past or concurrent histories of other neoplasms within 5 years (except for curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix uteri) were excluded. Patients with active uncontrolled infections or other serious conditions such as severe heart disease, uncontrollable hypertension, active gastric or duodenal ulcers, diabetes mellitus, or myocardial infarction within the preceding 6 months were also excluded.

The trial was conducted at two participating institutions in South Korea. Each local Institutional Review Board approved the protocol prior to study initiation. All patients provided written informed consent to indicate that they were aware of the investigative nature of this study.

Pretreatment evaluations

The baseline evaluations performed in all patients included medical history, physical examination, ECOG PS, complete blood counts with differential, serum chemistry and electrolytes, creatinine clearance, cancer antigen 19-9 (CA19-9), urine analysis, electrocardiography, chest X-ray, and three-dimensional computed tomography (3D CT). Brain imaging was performed if brain metastasis was suspected clinically.

Treatment scheme

The treatment consisted of intravenous gemcitabine (1,000 mg/m^2 over 30 min on days 1 and 8) and oral S-1 (40 mg/m^2 twice daily on days 1–14 of each cycle). Patients with a body-surface area (BSA) of <1.25 m^2, 1.25–1.5 m^2, and ≥1.5 m^2 received 80, 100, and 120 mg of S-1 daily, respectively. The treatment was repeated every 3 weeks. Although nine cycles of chemotherapy were planned, additional treatments could be administered at the physician's discretion. Chemotherapy could be terminated earlier in the event of objective disease progression, unacceptable toxicity, or at the patient's request.

Standard antiemetic prophylaxis using intravenous or oral 5-hydroxytryptamine-3 antagonists was administered before and after chemotherapy. Granulocyte colony-stimulating factor (G-CSF) was used to treat neutropenic events, but prophylactic G-CSF was not allowed in patients who experienced a neutropenic event in the previous cycle.

Dose modifications

Dose modifications were made according to the guidelines of the study protocol. The next cycle of treatment was begun only when the neutrophil count was ≥1,500/μL and the

platelet count was ≥100,000/μL. The treatment was delayed in the event of grade 3/4 non-hematologic toxicities until the condition resolved to grade ≤1. The dose of gemcitabine was reduced by 25 % of the initial dose for related grade 3 toxicities or the second occurrence of the same grade 2 toxicities. The dose of S-1 was reduced by 20 mg/day for related grade 3 toxicities or for the second occurrence of the same grade 2 toxicities. The dose of gemcitabine was reduced by 50 % of the initial dose for related grade 4 toxicities, the second occurrence of the same grade 3 toxicities, or the third occurrence of the same grade 2 toxicities. The initial dose of S-1 was reduced by 40 mg/day for related grade 4 toxicities, the second occurrence of same grade 3 toxicities, or the third occurrence of the same grade 2 toxicities. Treatment was discontinued if, despite the dose reduction, the same toxicity occurred for a fourth time at the same grade 2, a third time at same grade 3, or a second time at the same grade 4. In addition, the patient was removed from the study if the toxicity had not improved to grade 0 or 1 after 3 weeks. The dose reduction was maintained in subsequent cycles.

Response and toxicity evaluation

The RECIST guidelines were used to evaluate the tumor response [13]. An independent response review committee evaluated the tumor responses every two cycles using 3D CT. All complete and partial responses were confirmed by a second assessment at least 4 weeks later. Patients who received fewer than two full cycles of chemotherapy were considered ineligible for tumor response evaluation. After completion of the study treatment, all patients were followed up every 3 months until disease progression or death.

Toxicity was evaluated and recorded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (NCI-CTCAE), version 3.0. All patients who received at least one dose of treatment were included in the toxicity assessment. For the toxicity analysis, the worst data for each patient from all of the chemotherapy cycles were used.

Statistical analysis

This trial was a phase II study of combination chemotherapy using GS. The primary end point was ORR, and the secondary end points were OS, progression-free survival (PFS), and toxicity. According to the optimal two-stage phase II study design by Simon et al. [14], 34 patients should be enrolled to test the null hypothesis that the true ORR is 15 % versus the alternative hypothesis that the true ORR is at least 35 % at a significance level of 0.05 with a power of 80 %. If one or more responses were observed among nine patients in the first stage, the study would be continued and 25 additional patients would be included. Since the dropout rate was assumed to be 10 %, the calculated number of patients was 38.

The intention-to-treat (ITT) population included all patients, and the per-protocol (PP) population excluded the patients who received <6 weeks of treatment for reasons other than progressive disease or death or <50 % of the anticipated treatment during the first 6 weeks of the trial. The response and toxicity data were analyzed using simple descriptive statistics. PFS was calculated from the first day of the chemotherapy until the first date of documented disease progression or death from any cause. OS was calculated from the first day of chemotherapy until the date of death. The response duration was defined as the time from the date of first documented partial or complete response until the documented date of disease progression. PFS and OS were estimated using the Kaplan–Meier method.

Results

Patient characteristics

Between November 2005 and 2010, a total of 38 patients who met the inclusion criteria were enrolled into this study and signed informed consent forms. The demographic and pathological characteristics of the 38 patients are described in Table 1. The median patient age was 60.5 years (range 44–71), and 23 patients (60.5 %) were male. All patients had good PS (ECOG PS 0 or 1) and metastatic disease. Nineteen patients (50.0 %) had experienced disease recurrence after prior resection with curative intent. Fourteen patients had received adjuvant chemotherapy or concurrent chemoradiation therapy. All individuals were treated with intravenous 5-FU, except for two patients who received capecitabine as adjuvant chemotherapy. The primary tumor site was the gallbladder in 12 (31.6 %), intrahepatic and extrahepatic bile ducts in 23 (60.5 %), and ampulla of Vater in 3 (7.9 %) patients.

Efficacy

Thirty-four patients were eligible for response evaluation after two patients withdrew their consent and two patients were lost to follow-up before completing the first cycle. The tumor responses of all patients are summarized in Table 2. One patient achieved a complete response (CR), and six experienced a partial response (PR). The ORR was 20.6 % (95 % CI 8.5–36.7) in the PP population and 18.4 % (95 %CI 6.1–30.7) in the ITT population, with a median response duration of 10.8 months (95 %CI 5.3–16.2). Nineteen patients had stable disease (SD), and the disease control rate (DCR) was 76.5 % (95 %CI 60.0–87.6) in the PP population. Four of the fourteen patients who

Table 1 Patient characteristics

Characteristics	No. of patients (%)
Total number of patients	38
Gender	
Male	23 (60.5)
Female	15 (39.5)
Age, years	
Median	60.5
Range	44–71
ECOG performance status	
0	23 (60.5)
1	15 (39.5)
Location of primary tumor site	
Gallbladder	12 (31.6)
Intrahepatic bile duct	2 (5.3)
Extrahepatic bile duct	21 (55.2)
Ampulla of Vater	3 (7.9)
Histology	
Well differentiated	6 (15.8)
Moderately differentiated	12 (31.6)
Poorly differentiated	6 (15.8)
Unknown	14 (36.8)
Prior surgery	
Curative	19 (50.0)
Palliative	1 (2.6)
No surgery	18 (47.4)
Prior adjuvant therapy	
Chemotherapy	7 (18.4)
Chemoradiation therapy	7 (18.4)
Radiotherapy	2 (5.3)
No adjuvant therapy	22 (57.9)
Metastatic site	
Liver	19 (50.0)
Lung	6 (15.8)
Lymph node	15 (39.5)
Peritoneum	10 (26.3)
Bone	3 (7.9)
Number of metastatic sites	
1	23 (60.5)
≥2	15 (39.5)

ECOG Eastern Cooperative Oncology Group

Table 2 Analysis of the response (assessed by an independent response review committee)

	No. of patients (%)	95 % Confidence interval
Response		
Complete response	1	
Partial response	6	
Stable disease	19	
Progressive disease	8	
Not evaluable	4	
Objective response rate		
Per-protocol population	7 (20.6)	8.5–36.7
Intention-to-treat population	7 (18.4)	6.1–30.7
Disease control rate		
Per-protocol population	26 (76.5)	60.6–87.6
Intention-to-treat population	26 (68.4)	52.5–80.9
Median time to response (months)	1.5	1.4–1.7
Median duration of response (months)	10.8	5.3–16.2

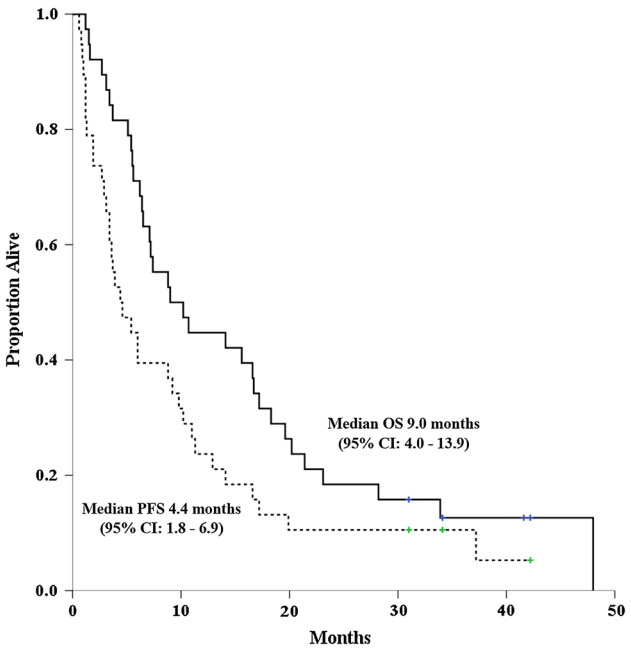

Fig. 1 Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS). *CI* confidence interval

received 5-FU or capecitabine as an adjuvant treatment had a PR, and three of the twenty chemotherapy-naïve patients exhibited a CR or PR. However, there was no significant difference in response rates between the above two groups in the PP population (28.6 % vs. 15.0 %, $p = 0.41$).

At the time of the analysis, the median follow-up duration was 9.5 months, and four patients were still alive. Of all the 38 enrolled patients, the median PFS was 4.4 months (95 %CI 1.8–6.9), the median OS was 9.0 months (95 %CI 4.0–13.9), and the 1-year survival rate was 44.7 % (95 CI 29.0–61.5; Fig. 1). Among the various clinical parameters, univariate analysis indicated that old age, worse PS, initial metastatic disease, liver metastasis, and no disease control were poor prognostic factors for OS (Table 3). Multivariate analysis revealed that patients with disease that was

Table 3 Univariate analysis of the prognostic variables for survival

Clinical Parameter	No. of patients	Median PFS (months)	*P*	Median OS (months)	*P*
Sex					
Male	23	4.6	0.582	10.2	0.806
Female	15	3.9		9.0	
Age					
<65	26	5.4	0.046	15.6	0.022
≥65	12	3.4		6.2	
ECOG performance status					
0	23	6.0	0.125	16.6	0.004
1	15	3.4		5.6	
Disease presentation					
Recurrent after operation	20	6.0	0.005	19.6	0.000
Metastatic initially	18	2.9		6.2	
Primary site					
GB	12	4.6	0.160	9.0	0.259
Non-GB	26	3.9		10.7	
Liver metastasis					
Presence	19	3.7	0.010	7.2	0.007
None	19	9.8		16.7	
Peritoneal metastasis					
Presence	10	2.9	0.232	3.4	0.062
None	28	5.4		14.1	
No. of metastatic sites					
1	23	5.4	0.549	10.7	0.227
2 or more	15	4.4		7.4	
Disease control					
Yes	26	6.0	0.000	16.6	0.000
No	12	1.2		3.4	

PFS progression-free survival, *OS* overall survival, *ECOG* Eastern Cooperative Oncology Group, *GB* gallbladder

refractory to chemotherapy or initial metastatic disease experienced shorter survival (Table 4).

Safety

Thirty-five patients who received at least one dose of chemotherapy were evaluated for toxicities. Most of the grade 3/4 toxicities were hematological, as shown in Table 5. Grade 3/4 hematological toxicities were observed in 13 patients (37.1 %): anemia in 2 (5.7 %), neutropenia in 9 (25.7 %), and thrombocytopenia in 2 (5.7 %). One patient experienced a grade 3 febrile neutropenia without any documented infection. The non-hematological toxicities were generally mild and not usually dose-limiting. Only five patients (14.3 %) experienced grade 3 non-hematological toxicities. Four patients (11.4 %) suffered a grade 3 hepatic toxicity. One of the four was dropped from the study because of delayed recovery, and one experienced grade 3 anorexia. One patient experienced grade 3 renal toxicity with proteinuria and hematuria. Grade 1 hand-foot syndrome (HFS) developed in two patients (5.7 %).

Table 6 summarizes the delivery of gemcitabine and S-1. Overall, the enrolled patients received 208 cycles of chemotherapy (median four, range 1–21). Seven patients completed nine or more cycles of chemotherapy. Three patients underwent dose reduction, and 21 experienced treatment delays. Four patients were dropped from the study because of treatment delays, most of which were due to grade 3/4 neutropenia, leukopenia, or thrombocytopenia. The mean relative dose intensity (ratio of the dose received to the dose planned) of GS for all the administered cycles was 0.84 (95 %CI 0.80–0.88) and 0.79 (95 %CI 0.74–0.84), respectively. The median relative dose intensity of GS for all the administered cycles was 0.86 (95 %CI 0.80–0.91) and 0.75 (95 %CI 0.67–0.83), respectively.

Discussion

The present study was conducted to evaluate GS combination therapy for the treatment of metastatic BTC. Several previous trials evaluated GS combination in patients with

Table 4 Multivariate analysis of the prognostic variables for survival

Clinical parameter	β	P	Hazard ratio
Disease presentation			
Recurrent after operation			
Metastatic initially	1.755	0.001	5.782
Disease control			
Yes			
No	1.099	0.007	3.000

Table 5 Observed adverse events according to number of patients

Event	Number of patients ($n = 35$)				
	NCI-CTCAE grade, version 3.0				
	1	2	3	4	3/4 %
Leukopenia	0	11	8	2	28.6
Neutropenia	9	4	7	2	25.7
Anemia	20	13	2	0	5.7
Thrombocytopenia	9	3	2	0	5.7
Febrile neutropenia	0	0	1	0	2.9
Anorexia	15	2	1	0	2.9
Nausea	14	3	0	0	0
Vomiting	4	1	0	0	0
Diarrhea	3	2	0	0	0
Constipation	6	0	0	0	0
Stomatitis	8	0	0	0	0
Myalgia	3	0	0	0	0
Neuropathy	1	0	0	0	0
Asthenia	5	2	0	0	0
Alopecia	1	0	0	0	0
Skin rash	1	0	0	0	0
Itching	12	0	0	0	0
Edema	1	0	0	0	0
Hand-foot syndrome	2	0	0	0	0
Hyperbilirubinemia	6	7	4	0	11.4
Abnormal AST/ALT	18	4	1	0	2.9
Abnormal ALP	17	5	2	0	5.7
Azotemia	0	1	1	0	2.9
Proteinuria	5	0	1	0	2.9
Hematuria	3	0	1	0	2.9

NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

BTC, all of which were conducted in Japan. The treatment schedules differed slightly from that used in the current study, in that either 1,000 mg/m^2 gemcitabine was administered on days 1 and 15 and 80 mg/m^2 S-1 was given daily for 14 consecutive days every 4 weeks, or 1,000 mg/m^2 gemcitabine was administered on days 1 and 8 and

Table 6 Dose administration

No. of cycles	208
Median	4 (range 1–21)
Mean ± SD	5.6 ± 5.2
No. of cycles with dose reduction	
1 level dose reduction	11
2 level dose reduction	1
No. of cycles with delay	53
No. of patients	38
No. of patients with dose reduction	
1 level dose reduction	2
2 level dose reduction	1
No. of patients with delay	21
Duration (range)	6–20 days
Relative dose intensity for gemcitabine	
Mean	0.84 (95 % CI, 0.80–0.88)
Median	0.86 (95 % CI, 0.80–0.91)
Relative dose intensity for S-1	
Mean	0.79 (95 % CI, 0.74–0.84)
Median	0.75 (95 % CI, 0.67–0.83)

SD standard deviation, *CI* confidence interval

60 mg/m^2 S-1 was administered daily for 14 consecutive days every 3 weeks [9–12]. The ORRs in the current study were 20.6 % in the PP group and 18.4 % in the ITT group, with a median PFS and OS of 4.4 and 9.0 months, respectively. The mean relative dose intensity of GS was 84 % and 79 %, respectively. Although the regimen in this study was slightly more intensive than was that in other trials of GS regimens, the results obtained regarding efficacy in the current study were not better than previous studies with respect to ORR and median OS. Differences in the patient populations might explain these discrepancies. All patients enrolled in the present study had metastatic disease; however, 29–48 % of the patients in other trials had locally advanced unresectable or relapsed cancers, which have better prognosis than does metastatic disease.

The efficacy results of this study were slightly inferior to those obtained in the ABC-02 study using a GC regimen as the first-line chemotherapy for BTC [5]. It reported an ORR of 37 %, a DCR of 81.4 %, and a median PFS of 8.0 months. However, the incidence of grade 3/4 nonhematologic toxicities, such as nausea, vomiting, fatigue, and infection, was much lower for the GS regimen used in the current study. In addition, in this previous study, the GC regimen consisted of 25 mg/m^2 cisplatin and 1,000 mg/m^2 gemcitabine on days 1 and 8 every 3 weeks and required at least a 2 h infusion time, whereas the GS regimen in the current study required only a 30-min infusion for gemcitabine. Therefore, the current GS regimen might be more convenient for patients, particularly in the outpatient clinic.

In the current study, most of the grade 3/4 hematological toxicities were leukopenia (28.6 %) and neutropenia (25.7 %), which often led to the suspension of chemotherapy on day 8. Specifically, more than one-third of the chemotherapy cycles were delayed, and 24 patients (63.2 %) experienced such a delay. Interestingly, the incidence of grade 3/4 neutropenia was less than in previous trials that used a 3-week regimen. The reason for this is unclear, but the suspension of chemotherapy due to mild leukopenia or neutropenia on day 8 might prevent severe neutropenia. Most patients recovered well from these toxicities, and only three patients received a dose reduction. The delayed chemotherapy reduced the mean dose intensity of GS to 0.84 and 0.79, respectively. Aside from hyperbilirubinemia, most non-hematological toxicities were mild and manageable, consistent with the findings of previous trials [10, 12].

In previous phase II studies, the combination of gemcitabine and another oral fluoropyrimidine, capecitabine, yielded an ORR of 25–32 % [15–18]. Although caution should be taken when comparing the results of single-arm phase II studies, the efficacy of gemcitabine and capecitabine appears similar to that of GS. However, HFS was observed less frequently in the GS group.

Regarding quality of life, safety and convenience are critical for the choice of treatment. The combination therapy including S-1 has a major advantage over continuous 5-FU infusion since oral administration is convenient and does not require an implanted catheter, which can cause serious adverse events.

Current guidelines recommend the GC combination as the standard of care for patients with advanced BTC. However, the GS combination might offer a good alternative treatment for patients with BTC who cannot tolerate cisplatin due to old age, neuropathy, nephropathy, or allergic reactions.

In conclusion, the GS combination chemotherapy exhibited acceptable efficacy and favorable toxicity profiles in patients with BTC. Therefore, it might be a reasonable alternative therapeutic strategy for some of these patients, and comparative clinical trials with reference regimens are warranted to confirm the potential of the GS regimen in patients with metastatic BTC.

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Conflict of interest None.

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