

ORIGINAL ARTICLE

Multicentre, phase II study of gemcitabine and S-1 in patients with advanced biliary tract cancer: TG1308 study

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Abstract

Background & Aims: Gemcitabine plus cisplatin (GC) remains the standard, frontline therapy for advanced biliary tract cancer (ABTC). The JCOG1113 study suggested that gemcitabine plus S-1 (GS) had noninferior median overall survival and comparable incidence of significant neutropenia as compared to GC treatments. This study evaluates the efficacy and safety of a modified GS regimen.

Methods: The eligible patients with chemo-naïve, measurable ABTC received 800 mg/m² of gemcitabine on day 1 and 80 mg/m²/day of S-1 (80/100/120 mg for patients with body surface <1.25/ ≥1.25 and <1.5/ ≥1.5 m² respectively). The primary endpoint was the 12-week disease control rate (12-week DCR: objective response and stable disease ≥ 12 weeks). Per the $p_0 = 40\%$ and $p_1 = 60\%$ ($\alpha/\beta = 0.05/0.2$) assumption, Simon's optimal two-stage design indicated 12-week DCR in ≥ 24 of 46 evaluable patients for significant activity. Tumour responses were assessed every 6 weeks.

Results: Fifty-one patients were enrolled and most of them had intrahepatic cholangiocarcinoma (64.7%), metastatic disease (84.3%) and disease-related symptoms (82.4%). On intention-to-treat analysis, 11 (21.6%) patients showed partial response, whereas 21 (41.2%) showed stable disease ≥ 12 weeks. The progression-free and overall survival were 5.4 months (95% confidence interval [CI]: 3.5-7.0), and 12.7 months (95% CI: 6.1-15.6) respectively. The study met its primary endpoint with a 12-week DCR of 69.6% in 46 evaluable patients. Grade 3/4 treatment-related adverse event-occurred in < 6% of patients of all individual items. The mean dose intensities of S-1 and gemcitabine were 87.1% and 92.5% respectively.

Conclusions: Modified GS showed moderate efficacy with a favourable safety profile in ABTC patients, thus mandating further assessment.

Abbreviations: ABTC, advanced biliary tract cancer; ALT, alanine transaminase; AVC, ampulla of Vater cancer; BSA, body surface area; BTC, biliary tract cancer; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; CR, complete response; DCR, disease control rate; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; GC, gemcitabine and cisplatin; GS, gemcitabine and S-1; HR, hazard ratio; IHCC, intrahepatic cholangiocarcinoma; ITT, intention-to-treat; mFOLFOX, modified oxaliplatin and 5-FU plus leucovorin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PP, per-protocol; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; SLOG, GS plus oxaliplatin and leucovorin; TCOG, Taiwan Cooperative Oncology Group; ULN, upper limit of normal.

Jen-Shi Chen, Yan-Shen Shan, and Li-Tzong Chen contributed equally to the manuscript.

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KEYWORDS

biliary tract cancer, gemcitabine, S-1

1 | BACKGROUND

Biliary tract cancers (BTCs) are classified as intrahepatic cholangiocarcinoma (IHCC), extrahepatic cholangiocarcinoma (EHCC), gallbladder cancer (GBC), and ampulla of Vater cancer (AVC) based on the anatomic origin. The incidence of BTC is increasing globally and generally higher in Asian countries than in Western countries.¹ According to the Taiwan Cancer Registration, 1637 new, cyto-/pathologically proven cases of biliary tract adenocarcinoma were reported in 2016, including 837 and 800 cases of IHCC and EHCC/GBC respectively.² Complete surgical resection remains the mainstay of treatment for patients with early-stage disease.³ However, most patients present with unresectable, advanced BTC (ABTC) at diagnosis,⁴ and intravenous administration of 1000 mg/m² of gemcitabine plus 25 mg/m² of cisplatin on days 1 and 8, every 21 days (GC regimen) has been considered the standard frontline therapy according to the UK ABC-02 and Japanese BT-22 studies.⁵⁻⁷ However, treatment with GC requires vigorous hydration and administration of potent antiemetics to prevent cisplatin-related adverse events,⁷ and results in grade 3/4 neutropenia significantly frequently in the Asian population (56.1% in BT-22 and 25.3% in ABC-02).^{5,6}

S-1, the newer-generation oral fluoropyrimidine, was approved for treatment of patients with ABTC in Japan in 2007 on the basis of the results of a multicentre phase II trial, with an objective response rate (ORR) of 35% and median progression-free survival (PFS) and overall survival (OS) rates of 3.7 and 9.4 months respectively.⁸ In the randomised phase II JCOG0805 study, patients treated with GS, comprising gemcitabine (1000 mg/m² on days 1 and 8) plus a reduced dose of S-1 (60 mg/m², 60/80/100 mg/day on the basis of the body surface area [BSA]) on days 1-14 every 3 weeks showed better median OS (12.5 months vs 9.0 months) than those treated with S-1 monotherapy at the regular dose (80 mg/m², 80/100/120 mg/day based on BSA) on days 1-28 every 6 weeks.⁹ In a subsequent randomized phase III JCOG1113 trial, patients treated with GS showed non-inferior

Lay Summary/Key Points

The modified GS regimen showed acceptable treatment efficacy and favourable safety and thus can be considered an alternative doublet regimen or backbone regimen to develop a triplet regimen for the treatment of patients with advanced biliary tract cancer.

median OS compared with those treated with GC (15.1 months vs 13.4 months, hazard ratio [HR]=0.945 with one-sided, non-inferiority $P = .046$),¹⁰ validating the GS regimen as an alternative standard of care for Japanese patients with ABTC.

Despite being more effective, the treatment with GS resulted in consistent 60% of grade 3/4 neutropenia, and required frequent dose modification in both the JCOG0805 and JCOG1113 studies.^{9,10} In the GS arm of JCOG1113, the relative mean dose intensity (DI) of gemcitabine and S-1 was 76.2% and 75.3% respectively.¹⁰ Furthermore, comparison of the monotherapy arm in the BT-22 and JCOG0805 studies indicated that patients treated with S-1 had comparable but numerically better ORR (17.4% vs 11.9%), median PFS (4.2 months vs 3.7 months), median OS (9.0 months vs 7.7 months), and safety profiles (grade 3/4 neutropenia, 4.0% vs 38.1%) than those treated with gemcitabine.^{5,10} Therefore, considering S-1 to have better a therapeutic index than that of gemcitabine, we investigated whether the modified GS regimen, comprising higher DI of S-1 and lower DI of gemcitabine can improve the therapeutic index of GS in ABTC. The aim of the current phase II trial was to evaluate the efficacy and safety of biweekly gemcitabine in combination with a full 80 mg/m²/day (80/100/120 mg/day by BSA) dose of S-1 on days 1-10 every 2 weeks, termed the 'modified GS' regimen, as frontline treatment in patients with ABTC. The planned DI of S-1 would be 400 mg/m²/wk in the current modified GS regimen, as opposed to 373 mg/m²/wk in S-1 monotherapy arm of the JCOG0805 and 280 mg/m²/wk in GS arm of both the JCOG0805 and JCOG1113 studies.^{9,10}

2 | PATIENTS AND METHODS

2.1 | Patient eligibility

The inclusion criteria for patients were as follows: (a) histologically confirmed adenocarcinoma of the biliary tract that was unresectable or metastatic, including IHCC, EHCC, GBC, and AVC, with at least 1 measurable lesion according to the response evaluation criteria in solid tumours (RECIST) version 1.1; (b) patient age ≥ 20 years; (c) an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1; (d) adequate bone marrow, hepatic, and renal functions (absolute neutrophil count $\geq 1500/\mu\text{L}$, platelets $\geq 100\,000/\mu\text{L}$, haemoglobin $\geq 9\text{ g/dL}$, serum total bilirubin level ≤ 1.5 times the upper limit of normal [ULN] and $< 2\text{ mg/dL}$ [or $< 3\text{ mg/dL}$ if biliary drainage was present], alanine transaminase (ALT) level ≤ 3 times the ULN [or ≤ 5 times the ULN in the presence of liver metastasis], and creatinine clearance (Ccr) $\geq 60\text{ mL/min}$ calculated by 24-hour urine collection or the Cockcroft-Gault formula); and (e) no prior chemotherapy or radiotherapy. All the patients provided written informed consent as a condition for enrolment.

The exclusion criteria were as follows: (a) the presence of grade 2 or above ascites, pleural effusion, or diarrhoea; (b) previous or current brain metastasis; (c) uncontrolled active infection or other concomitant serious disease; (d) pregnancy or breast-feeding; (e) active cardiopulmonary disease, history of ischaemic heart disease, and/or serious concomitant systemic disorders; and (f) concurrent malignancy, except for those with adequately treated in situ carcinoma of the cervix, adequately treated basal cell carcinoma of the skin, or a disease-free status for ≥ 5 years after initial curative treatment for any prior malignancy.

This phase II study was conducted at four member hospitals of the Taiwan Cooperative Oncology Group (TCOG). The protocol was approved by the independent ethics committees of the individual participating hospital and National Health Research Institutes, and the Department of Health, Executive Yuan, Taiwan. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation 'Good Clinical Practice' guideline. The study is registered at ClinicalTrials.gov (NCT02425137).

2.2 | Study treatment and dose modification

The modified GS regimen consisted of intravenous infusion of 800 mg/m^2 gemcitabine on day 1 plus 40 mg/m^2 oral S-1 twice daily after meals, accounting for a total daily dose of $80/100/120\text{ mg}$ on the basis of the BSA ($<1.25/\text{m}^2$; $\geq 1.25/\text{m}^2$ and $< 1.5/\text{m}^2$; or $\geq 1.5/\text{m}^2$), administered on days 1-10 every 2 weeks/cycle. Premedication included an intravenous bolus injection of metoclopramide and chlorpheniramine with or without dexamethasone. Prophylactic granulocyte-colony stimulating factor was administered in only those patients with either grade 4 or complicated neutropenia after the first treatment cycle. The subsequent cycle could be started only

if the following criteria were met on day 1: neutrophil count $\geq 1500/\text{mm}^3$, platelet count $\geq 75\,000/\text{mm}^3$, total bilirubin ≤ 2 times the ULN, ALT ≤ 3 times the ULN, and all other non-haematological toxicities recovered to $<$ grade 2. If the patient failed to meet these criteria before commencing the next cycle, the chemotherapy may be delayed by up to 2 weeks. If febrile or grade 4 neutropenia, grade 4 thrombocytopenia (or grade 3 that required platelet transfusion), or grade 3-4 non-haematological toxicities, which were considered to be gemcitabine-related, occurred, then the subsequent dose of gemcitabine would be reduced by 200 mg/m^2 . If grade 3-4 diarrhoea, stomatitis, rash, or non-haematological toxicities associated with S-1 occurred, then the subsequent S-1 dose would be reduced by 20 mg/day . Dose reduction of either drug was allowed only twice, with the permitted nadir dose being 400 mg/m^2 for gemcitabine and 60 mg/day for S-1. However, no further dose reescalation was permitted. The treatment regimen was continued until disease progression, unacceptable toxicity, patient refusal, adoption of other systemic or definitive local therapy, or death. The actual DI was defined as the total amount of drug administered per week divided by the baseline BSA of an individual patient ($\text{mg/m}^2/\text{wk}$) during the 12 cycles from the start of chemotherapy, with reference to the JCOG0805 study.⁹

2.3 | Pre-treatment and follow-up evaluation

Pre-treatment evaluation included a review of the patient's medical history, physical examination, assessment of blood cell counts, serum biochemical tests, electrocardiography, chest radiography, and contrast-enhanced computed tomography or magnetic resonance imaging. Physical examinations and blood tests were scheduled on day 1 of each treatment cycle. The levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were measured at baseline and every 2 cycles thereafter. Radiographic follow-up was performed every 6 weeks. The tumour response would be assessed based on the RECIST version 1.1 with confirmation of objective response using 2 successive imaging studies. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 4.0. The survival status was checked at least monthly after the end of treatment until death or loss to follow-up.

2.4 | Statistical analysis

The primary endpoint was the 12-week DCR, defined as the percentage of patients with complete/partial response [CR/PR] or stable disease [SD] for ≥ 12 weeks. The secondary endpoints included objective response rate (ORR), PFS, OS, and safety profiles. Considering the DCR of patients treated with gemcitabine alone was 50% at 6 weeks in BT-22 and 45% at 8 weeks in our previous study,^{5,11} the p_0 was set as 40% of the 12-week DCR in this study. The sample size was calculated on the basis of Simon's optimal two-stage design of $p_1 = 60\%$, with a significance level of 0.05 and a power of 80%.¹² Sixteen evaluable patients will be accrued in the first stage; if 8 or more of them have

CR/PR or SD \geq 12 weeks, the study would be extended to the second stage, in which 30 additional evaluable patients would be accrued. The null hypothesis would be rejected if \geq 24 patients of the 46 evaluable patients achieve CR/PR or SD at \geq 12 weeks. All efficacy analyses were applied to the intention-to-treat (ITT) population, wherein the main assessment primary endpoint of \geq 12-week DCR, depending on the per protocol (PP) population, was defined as patients who completed at least 2 treatment cycles and underwent a scheduled follow-up tumour assessment. The safety population consisted of subjects who received at least one dose of treatment. The PFS and OS were estimated using the Kaplan-Meier method. PFS was calculated from the date of enrolment to the date of first radiographically evident disease progression or death or was censored at the subsequent date for patients who withdrew informed consent, underwent either conversion surgery or consolidation local radiotherapy, or received other chemotherapy agent(s) at the discretion of the physician in charge before documentation of disease progression, whichever occurred first. The OS was defined as the time from the initiation of therapy to the date of death from any cause or censored at the date of final follow-up for survivors and those loss of follow-up. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A two-sided *P* value $<$ 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

A total of 51 patients were enrolled between May 2015 and May 2017. The baseline demographics of all patients are summarised in Table 1. The patients had a median age of 63 years (range, 32-77 years), 29 were men (57%), 42 (82.4%) had an ECOG PS of 1, 43 (84.3%) had metastatic disease, and 33 (64.7%) and 10 (19.6%) had primary IHCC and GBC respectively. Fourteen of the 51 patients (28%) had recurrent disease after a previous curative surgery.

3.2 | Treatment delivery

At the data cut-off date (31 May 2017), one patient remained on treatment and 13 were alive with a median follow-up duration of 13.3 months (95% confidence interval [CI], 8.0-18.6 months). The main reasons for discontinuation were disease progression in 32 (62.7%), intolerable toxicities in 9 (17.6%), and withdrawal of informed consent in 5 patients (9.8%). In 4 (7.8%) patients, treatment was discontinued at the investigator's discretion. The starting dose of S-1 was 120 mg/day in 38 patients (74.5%) and 100 mg/day in the rest. Patients with a starting S-1 dose of 120 and 100 mg/day had a mean BSA of 1.74 m² (range, 1.51-2.72 m²) and 1.40 m² (range, 1.27-1.49 m²) respectively. The average initial dose of S-1 was 35.1 mg/m² (range, 26.4-39.8 mg/m²). The median number of treatment cycles was 10.5 (range, 3-48). Ten (20%) and 17 (33%) patients required

TABLE 1 Baseline demographics and clinical characteristics (N = 51)

	ITT population
Age (y)	
Median (range)	63 (32-77)
<65	34 (66.7)
\geq 65	17 (33.3)
Gender	
Male	29 (56.9)
Female	22 (43.1)
ECOG performance status	
0	9 (17.6)
1	42 (82.4)
Primary site	
Intrahepatic	33 (64.7)
Extrahepatic	5 (9.8)
Gallbladder	10 (19.6)
Ampulla vater	3 (5.9)
Disease status at entry	
Locally advanced	8 (15.7)
Distant Metastasis	43 (84.3)
Previous surgery	
Yes	14 (27.5)
No	37 (72.5)
Stent or drainage	
No	41 (80.4)
Yes	10 (19.6)
PTCD	5 (9.8)
Stent	5 (9.8)
Metastatic sites	
Liver	37 (72.5)
Lung	6 (11.7)
Lymph node	30 (58.8)
Bone	1 (2.0)
CA199 (U/mL)	
Median (range)	140 (9-516340)
CEA (ng/mL)	
Median (range)	3.1 (0.5-4070)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat.

gemcitabine and S-1 dose modification, respectively. The mean delivered DI was 305.5 mg/m²/wk (87.1% of planned DI) for S-1 and 369.8 mg/m²/wk (92.5% of planned DI) for gemcitabine.

3.3 | Treatment efficacy

Of the 16 evaluable patients in the first stage, 8 had \geq 12-week disease control, and thus met the criteria for proceeding to the second

stage. In the ITT population, inclusive of 46 evaluable and 5 non-evaluable patients, the best tumour responses were confirmed partial response in 11 (21.6%), stable disease in 27 (52.9%), and progressive disease or unevaluable status in 13 patients (25.5%). Furthermore, 32 (62.7%) patients had a DCR \geq 12-weeks. The median PFS was 5.4 months (95% CI, 3.5-7.0 months), as shown in Figure 1A, whereas the median OS was 12.7 months (95% CI, 6.1-15.6 months), with 1- and 2-year OS rates of 51% and 14% respectively (Figure 1B). Additionally, in the PP analysis that included the 46 evaluable patients only, the 12-week DCR was 69.6%, with a PFS and OS of 5.7 and 14.5 months respectively (Table 2).

3.4 | Toxicity

Of the 51 patients, the most common all grade treatment-related toxicities were anaemia (49%), anorexia (39.2%) and fatigue (35.3%), as summarised in Table 3. The incidence of grade 3/4 adverse events was < 6% for all individual items, including 5.9% for skin rashes and 3.9% each for neutropenia, thrombocytopenia, elevated ALT levels and hyperbilirubinemia. There was one possible treatment-related death that manifested as liver failure secondary to reactivation of hepatitis B virus infection after 4 cycles of treatment in a patient with a negative hepatitis B surface antigen serology test at study inclusion.

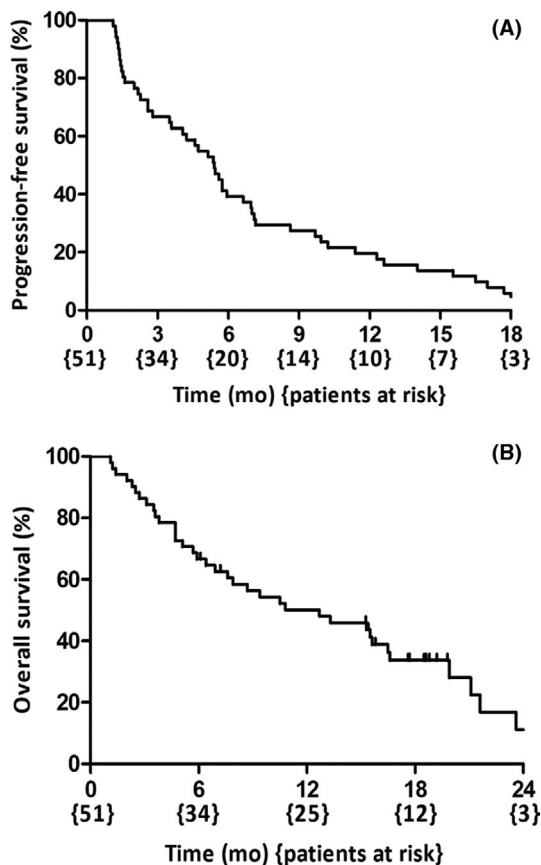


FIGURE 1 Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) in 51 patients in the ITT population

3.5 | Post-study treatment and evaluation of CA 19-9/CEA

Of the 46 patients in the PP cohort, 32 (69.6%) received post-study treatment. Among them, 16 patients (50%) received 5-fluorouracil and platinum-based regimens (oxaliplatin in 11 and cisplatin in 5), while 5 (15.6%) received a gemcitabine-based regimen. The other

TABLE 2 Efficacy results

	ITT (N = 51)	PP (N = 46)
Best overall response		
Complete response (CR)	0	0
Partial response (PR)	11 (21.6%)	11 (23.9%)
Stable disease (SD)	27 (52.9%)	27 (58.7%)
Progressive disease	8 (15.7%)	8 (17.4%)
Not evaluated	5 (9.8%)	0
Long-term DCR	32 (62.7%)	32 (69.6%)
Median PFS (mo, 95% CI)	5.4 (3.5-7.0)	5.7 (4.2-7.1)
Median OS (mo, 95% CI)	12.7 (6.1-15.6)	14.5 (7.6-16.6)

Abbreviations: CI, confidence interval; DCR, disease control rate; ITT, intention-to-treat; Long-term DCR, CR, PR and SD \geq 12 wks; OS, overall survival; PFS, progression-free survival; PP, per protocol.

TABLE 3 Treatment-related adverse events (N = 51)

	All grades		Grade 3/4	
	N	%	n	%
Haematological toxicities				
Leucopenia	5	9.8	1	2.0
Neutropenia	6	11.8	2	3.9
Febrile neutropenia	1	2.0	1	2.0
Thrombocytopenia	9	17.6	2	3.9
Anaemia	25	49.0	0	0
Non- haematological toxicities				
Anorexia	20	39.2	0	0
Fatigue	18	35.3	1	2.0
Nausea	7	13.7	0	0
Vomiting	7	13.7	0	0
Diarrhoea	9	17.6	1	2.0
Stomatitis	13	25.5	1	2.0
Elevated AST	5	9.8	1	2.0
Elevated ALT	3	5.9	2	3.9
Hyperbilirubinemia	2	3.9	2	3.9
Skin rash	12	23.6	3	5.9
Pruritus	11	21.6	0	0
Allergic reaction	4	7.8	1	2.0
Skin hyperpigmentation	15	29.3	0	0
Alopecia	3	5.9	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

treatments included radiotherapy with or without concurrent chemotherapy (N = 4), 5-FU monotherapy (N = 1), recruitment in clinical trial with tyrosine kinase inhibitor (N = 2), paclitaxel-based regimens (N = 2) and pembrolizumab (N = 1). One patient underwent salvage surgery involving a partial hepatectomy with lymph node dissection and adhesiolysis. Series follow-up data were available for 32 (69.6%) and 16 (34.8%) patients with elevated baseline CA 19-9 and CEA levels respectively. Of these, patients with a biomarker response, defined as a more than 50% decrease in tumour marker levels during the study treatment, had better therapeutic outcomes than did those without such a biomarker response. Of the former 32 patients, 17 (56.3%) patients with a CA 19-9 response showed a better ORR (41.2% vs 6.7%, $P = .041$), median PFS (9.9 months vs 5.3 months, $P = .114$), and median OS (19.9 months vs 6.6 months, $P = .001$) than did those without a CA 19-9 response (Table S1). Furthermore, of the latter 16 patients, 6 (37.5%) with a CEA response showed a better ORR (66.7% vs 10%, $P = .036$), median PFS (8.5 months vs 3.2 months, $P = .018$) and median OS (19.9 months vs 5.3 months, $P = .132$) than did those without a CEA response (Table S2).

4 | DISCUSSION

The modified GS regimen was designed to investigate whether the therapeutic index of GS can be improved by adjusting the dosing schedule and thus modifying the DI of the study drugs. The current study achieved its primary endpoint with a 12-week DCR of 69.6% in the PP population. Additionally, the secondary endpoints were favourable, and an excellent toxicity profile was observed. Upon administering 800 mg/m² of gemcitabine on day 1 and 80 mg/m²/day of S-1 on days 1-10 every 2 weeks, the mean relative DI achieved was 92.7% and 87.1% for gemcitabine and S-1 respectively. Assuming that patients in the GS arm in the JCOG1113 and JCOG0805 studies had a similar planned DI (280 mg/m²/wk),^{9,10} it appears that the mean DI for S-1 and gemcitabine in the TG1308 study was 44.7% higher (305.5 mg/m²/wk vs 211.1 mg/m²/wk) and 27.2% lower (369.8 mg/m²/wk vs 508.2 mg/m²/wk) than that in the GS arm in the JCOG1113 study, respectively.¹⁰ These findings could likely raise concerns regarding the numerically inferior therapeutic outcomes of the modified GS regimen when compared with those of the GS regimen used in JCOG1113, with the ORR, median PFS, and median OS being 21.6% vs 29.8%, 5.4 vs 6.8 months and 12.7 vs 15.7 months respectively. This discrepancy may partially be explained by differences in the study design and demographic characteristics of the patients recruited in the two studies. First, ORR required confirmation in the current study but not in JCOG1113. Second, in the GS arm of JCOG1113, 31% patients had an ECOG PS of 1 and 61% patients had metastatic disease, whereas in our study, these values were 82.4% and 84.3% respectively. Poorer OS had been reported in patients with metastatic disease under treatment with GS, both in the JCOG0805 and a Korean phase II studies, in which the median OS of patients with metastatic disease was 10.6 and 5.6 months (vs 13.0 and 16.6 months in those with locally

advanced disease) respectively.^{9,13} In our post hoc analyses, the median OS of patients with metastatic and locally advanced disease was 8.7 and 23.6 months, respectively, whereas that for patients with an ECOG PS of 1 and 0 was 7.9 and 16.5 months respectively (data not shown). The incidence of grade 3/4 neutropenia was significantly lower in those treated with the modified GS regimen, 3.9% vs 59.9-60.7% in the JCOG1113 and JCOG0805 studies and 25.7% in a Korean study, all of which used the GS regimen (Table S3).^{9,10,13} The results suggest that treatment with a biweekly modified GS regimen has a better therapeutic index and comparable efficacies to those of treatment with GS regimens used in previous ABTC studies, but a better safety profile.

Furthermore, the therapeutic efficacy of the modified GS regimen, an ORR of 21.6%, median PFS of 5.4 months, and median OS of 12.7 months, were comparable to those obtained with global standard GC regimens used in three Japanese ABTC trials, the BT-22, JCOG1113 and KHBO1401-MITSBA studies in which the median (range) ORR, median PFS, and median OS were 19.5% (15.0-32.4%), 5.8 months (5.5-5.8 months) and 12.6 months (11.2-13.4 months) respectively,^{5,10,14} these values were 25.5%, 8.0 months and 11.7 months respectively, in the ABC-02 study.⁶ However, the safety profile of the modified GS regimen was much better than that of conventional GC regimens, especially in studies conducted on Asian populations. The incidence of both grade 3/4 neutropenia and thrombocytopenia was 3.9% with the modified GS regimen, whereas it was 25.3% and 8.6%, respectively, in the ABC-02 study,⁶ with a median (range) incidence of 56.1% (48-60.8%) and 21% (16.4-39.0%), respectively, in the three Japanese studies mentioned above.^{5,10,14} These findings indicate that the modified GS regimen may serve as a gemcitabine-based doublet option in Asian patients with ABTC. It could also be a favourable regimen for borderline fit, cisplatin-ineligible or older patients because of advantages such as low peripheral neurotoxicity, low incidence of severe haematological toxicities, and no requirement for vigorous hydration, unlike in treatment with GC regimens. However, the delayed urinary excretion of 5-chloro-2,4-dihydroxypyridine, an inhibitor of the dihydropyrimidine dehydrogenase that degrades 5-FU, will lead to an increase in the area under the curve for 5-FU and associated grade 3/4 adverse events.¹⁵ Therefore, similar to cisplatin, S-1 should be cautiously administered in patients with renal function impairment. Furthermore, serum creatinine levels ≤ 1.2 mg/dL and creatinine clearance (Ccr) ≥ 50 mL/min were common inclusion criteria for clinical trials involving S-1, such as the JCOG1113 and GEST pancreatic cancer studies.^{10,16} The combination of gemcitabine plus oxaliplatin could be a better option than GC and the modified GS regimen in ABTC patients with moderate to severe renal function impairment.

The active compounds used for the treatment of ABTC are limited globally. However, S-1 has rarely, if ever, been tested in Caucasian ABTC patients because of the perception of relatively poor compliance and lower maximum tolerated and recommended S-1 doses in the Western population than in Asians. This has largely been attributed to population differences in polymorphisms of the CYP2A6 gene, which encodes an enzyme responsible for converting

tegafur to 5-FU, and the pharmacokinetics of oxanate, which inhibits the phosphorylation of 5-FU within the small intestinal mucosa related to gastrointestinal toxicities.¹⁷ However, a more detailed review of the literature does not support the notion that S-1 is a 'tough' drug for Caucasian cancer patients. In Western studies, the maximum tolerated dose of S-1 using a 3-4-weeks-on/1-week-off schedule has been reported to be 50 mg/m² daily or 30 mg/m² twice daily in previously treated patients, and 40 mg/m² in chemo-naïve patients, with the primary dose-limiting toxicity being grade 3/4 diarrhoea.¹⁸⁻²⁰ In a phase II study by the European Organisation for Research and Treatment of Cancer (EORTC) Early Clinical Trial Group that included chemo-naïve gastric cancer patients, 35 mg/m² of S-1 administered twice daily for 28 days every 5 weeks was well-tolerated, with grade 3 diarrhoea being observed in 12% of patients and 4% of treatment cycles.²¹ Furthermore, a recent randomized phase III trial, the SALTO study, which compared the compliance for first-line 30 mg/m² S-1 and 1000-1250 mg/m² capecitabine administered twice daily, with a 2-weeks-on/1-week-off schedule, showed that treatment with S-1 was associated with a significantly lower incidence of grade 3 hand-foot syndrome (4% vs 21%; $P = .003$), but a higher incidence of grade 3 anorexia (13% vs 3%; $P = .03$) than capecitabine in Dutch patients with metastatic colorectal cancer.²² While the incidence of grade 3/4 diarrhoea (16% vs 12%; $P = .65$) and therapeutic efficacy were comparable in both groups, the median relative DI was 95% and 88% for S-1 and capecitabine, respectively. With the unique dosing schedule of S-1, 120 mg/day for individuals with a BSA > 1.5 m², the initial dose would be 40, 35, and 30 mg/m² for patients with a BSA of 1.5, 1.71 and 2.0 m² respectively. In this study, the average initial dose of S-1 according to individual BSA was 35.1 mg/m² (range, 26.4-39.8 mg/m²), which was equivalent to the 35.9 mg/m² (range, 31.7-39.7 mg/m²) reported by Hirata et al.²³ In a recent retrospective analysis, the median BSA of 1650 Caucasian adult cancer patients was 1.86 m² (interquartile range, 1.68-2.00).²⁴ In the SALTO study in which 30 mg/m² of S-1 was administered twice daily, 75% of Caucasian patients would have an initial S-1 dose of more than 100 mg/day, the assigned dose for patients with a BSA ≥ 1.5 m² in Japanese GS studies.^{9,10,22} As S-1 is an anti-metabolite cytotoxic compound, the compliance to treatment with S-1 is expected to be schedule-dependent. In a previous trial for gastric cancer, the completion rates for 12 months of adjuvant S-1 at a dose of 80/100/120 mg/day with the conventional 4-weeks-on/2-weeks-off and the modified 2-weeks-on/1-week-off schedules were 49% and 89% respectively.²⁵ However, whether the 10-days-on and 4-days-off schedule can improve compliance with S-1 treatment and thus ensure the feasibility of the modified GS regimen in Caucasian patients warrants further investigation.

A recent trend has been to develop triplet chemotherapy regimens, such as GC combined with either S-1 or abraxane, as first-line treatment for ABTC.^{26,27} A Japanese phase III study showed a significantly improved ORR (41.5% vs 15%), longer median PFS (7.4 months vs 5.5 months, HR 0.75; $P = .0015$) and longer median OS (13.5 months vs 12.6 months, HR 0.79; $P = .046$) in patients receiving GC plus S-1 than in those receiving GC.¹⁴ In a single-arm phase II trial

involving patients with ABTC (N = 60), Shroff et al showed promising treatment efficacies (ORR of 45%, PFS of 11.8 months, and OS of 19.2 months) in patients receiving GC plus nab-paclitaxel.²⁷ A phase III trial, SWOG S1815, comparing the outcomes of treatment with GC plus nab-paclitaxel and GC alone in patients with newly diagnosed ABTC is currently underway. Furthermore, we have previously tested the triplet regimen of GS plus oxaliplatin and leucovorin (SLOG) in patients with advanced pancreatic cancer, and found that the treatment efficacy was encouraging, and the safety profile was acceptable.²⁸ The TCOG-T3217 (NCT03406299) randomised phase II trial, comparing SLOG and GC as first-line treatment for ABTC, is currently on-going. Owing to its favourable therapeutic index, the modified GS regimen is an ideal backbone chemotherapy for ABTC patients in combination with additional cytotoxic chemotherapies, molecular targeted agents, or immune checkpoint inhibitors. Our investigator-initiated phase II trial, TCOG-T1219, which examines the efficacy of the modified GS regimen plus nivolumab in patients with ABTC is currently underway (NCT04172402).

As for the post-study treatment in our study, platinum plus 5-fluorouracil was the most common regimen, especially in combination with oxaliplatin. The recent ABC-06 trial showed that a modified oxaliplatin and 5-FU plus leucovorin (mFOLFOX) regimen significantly improved the OS in patients showing disease progression after treatment with GC. Thus, mFOLFOX was proposed as the standard second-line regimen for the treatment of patients with ABTC.²⁹ Moreover since peripheral neuropathy is an adverse event noted in patients treated with both cisplatin (GC) and oxaliplatin (mFOLFOX), GS or a modified GS followed by mFOLFOX may be considered as a reasonable and favourable sequential therapeutic strategy.

5 | CONCLUSIONS

This modified GS regimen, which can easily be administered in an outpatient setting, shows acceptable efficacy with a favourable safety profile in Taiwanese patients with ABTC. Further studies with the modified GS regimen administered either alone in older or cisplatin-ineligible patients, except those with moderate to severe renal function impairment, or as backbone chemotherapy in combination with other potentially active agents for fit patients, are warranted.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

NJC, JSC, YSS, and LTC contributed to the protocol development and manuscript preparation. NJC, MHC, SHY, CH, CJY, JSC, YSS, and LTC enrolled the patients. NJC, YSS, HHT, YYS, and LTC collected and analysed data. All authors participated in data interpretation, final manuscript review and approval. JSC, YSS, and LTC are responsible for submission and publication decisions.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This trial was approved by the Institutional Review Board (IRB) of all four participating institutes with reference number: AB-CR-104-007, 103-7658A2, 2015-04-011AU, and 201412001MSA. All patients had signed informed consent forms.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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