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Real-world efficacy and safety of nab-paclitaxel plus gemcitabine-cisplatin in patients with advanced biliary tract cancers: a multicenter retrospective analysis

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Abstract

Background: A recent phase II trial reported prolonged survival in patients with advanced biliary tract cancer (BTC) following treatment with nab-paclitaxel plus gemcitabine-cisplatin (Gem/Cis/nab-P). We aimed to evaluate the clinical outcomes of Gem/Cis/nab-P in Asian patients with advanced BTC in a real-world setting.

Methods: We reviewed the data of patients who received Gem/Cis/nab-P for the management of advanced BTC between September 2019 and April 2021 at four institutes in Korea. Patients were classified into the Gem/Cis/nab-P and nab-P addition groups depending on the starting point of nab-P administration.

Results: A total of 178 patients treated with Gem/Cis/nab-P were included in the study. Of these, 43.8% had intrahepatic cholangiocarcinoma (CCA), 34.8% had extrahepatic CCA, and 21.3% had gall bladder cancer. A total of 117 (65.7%) patients received Gem/Cis/nab-P as the first-line treatment, while 61 (34.3%) were treated with gemcitabine-cisplatin-based chemotherapy followed by nab-P addition. The objective response rate (ORR) and disease control rate in all patients were 42.1% and 84.8%, respectively. The ORR in the Gem/Cis/nab-P group was 47.9%, while that in the nab-P addition group was 31.1%. The median progression-free survival and overall survival were 8.5 months [95% confidence interval (CI), 6.9–10.1] and 14.6 months (95% CI, 10.2–19.0), respectively. In patients who received Gem/Cis/nab-P as initial treatment, the median PFS was 9.4 months (95% CI, 7.9–10.9) and the median OS was not-reached (95% CI, not available). Anemia ($n = 42$, 23.6%), neutropenia ($n = 40$, 22.5%), and thrombocytopenia ($n = 16$, 9.0%) were the most common grade 3–4 toxicities. A total of 20 patients (11.2%) had conversions from unresectable to resectable disease and underwent surgery with curative intent.

Conclusion: Gem/Cis/nab-P showed favorable real-life efficacy and safety outcomes in Korean patients with advanced BTC, which was consistent with the phase II trial outcomes.

Keywords: biliary tract cancer, cisplatin, gemcitabine, nab-paclitaxel, real-world

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Introduction

Biliary tract cancer (BTC) is a rare gastrointestinal malignant neoplasm and includes intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, and gall bladder cancer (GBC). Curative surgical resection offers the only chance for cure. However,

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most patients with BTC are diagnosed at an unresectable stage.[1] Therefore, the survival outcomes of patients with advanced BTC remain dismal.[2,3] Furthermore, the rarity and heterogeneity of subtypes limit clinical trial progress in advanced BTC.

The combination of gemcitabine and cisplatin (Gem/Cis) has become the current standard for advanced BTCs since the landmark ABC-02 trial in 2010.[4] This trial demonstrated that the addition of cisplatin to gemcitabine improved survival outcomes compared with those with gemcitabine alone. However, the median overall survival (OS) of Gem/Cis chemotherapy is less than 1 year.[5–10] Recently, a triplet regimen of gemcitabine, cisplatin, and nab-paclitaxel (Gem/Cis/nab-P) showed promising results in a single-arm phase II multicenter study of 60 patients with advanced BTCs.[11] The median progression-free survival (PFS) and OS were 11.8 months and 19.2 months, respectively. The objective response rate (ORR) was 45%, and the disease control rate (DCR) was 84%. Grade 3 or higher toxicities were observed in 57% of patients, and 16% of patients withdrew due to adverse events. A phase III randomized clinical trial comparing Gem/Cis/nab-P against Gem/Cis is currently underway.

The incidence of BTC has been reported to be relatively high in eastern Asia.[12–14] However, the previous phase II study of Gem/Cis/nab-P triplet chemotherapy included only patients from the United States (US), and the differences and consequences arising from ethnicity remain unexplored.[11] Nonetheless, the off-label use of Gem/Cis/nab-P has been officially granted for patients with advanced BTC in designated centers by the Health Regulatory Agency of Korea. Therefore, we performed a multicenter retrospective analysis to evaluate the efficacy and safety of Gem/Cis/nab-P in patients with unresectable or metastatic BTC in a real-world setting.

Materials and methods

Patients

This was a retrospective, multicenter, noncomparative, observational study. We included patients treated with Gem/Cis/nab-P for advanced BTC between September 2019 and April 2021 at four referral cancer centers (CHA Bundang Medical Center, Yonsei Cancer Center, Ulsan University Hospital, and Samsung Changwon Hospital) in Korea. Patient characteristics, treatment history, and survival outcomes were reviewed. Gem/Cis/nab-P was administered predominantly for newly diagnosed patients based on the previous results of the phase II study, if the patient's performance status allowed.[11] Patients who were treated with Gem/Cis/nab-P as the first-line treatment were classified into the "Gem/Cis/nab-P group." Patients who were initially treated using the Gem/Cis-based regimen, which was subsequently changed to Gem/Cis/nab-P, were classified into the "nab-P addition group." Therefore, these patients were further divided into subgroups: "nab-P addition without progressive disease (PD) group" (addition of nab-P to Gem/Cis in the absence of disease progression) or "nab-P addition with PD group" (addition of nab-P in the presence of disease progression). In the "nab-P addition group", nab-P was added to the previous Gem/Cis-based chemotherapy according to the clinician's decision, and these treatment choices were made individually within the same hospital.

Treatment and response assessment

All patients received Gem/Cis/nab-P either at a high-dose (gemcitabine 1000 mg/m^2, cisplatin 25 mg/m^2, and nab-paclitaxel 125 mg/m^2) or as a reduced-dose (gemcitabine 800 mg/m^2, cisplatin 25 mg/m^2, and nab-paclitaxel 100 mg/m^2) as described in the phase II trial.[11]

The treatment dose was modified depending on the clinical situation at the discretion of the attending physician. Gem/Cis/nab-P treatment was continued until patients experienced intolerable toxicity or disease progression. Tumor responses were assessed once every 6–8 weeks using computed tomography or magnetic resonance imaging. The treating physicians assessed the treatment response according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. All treatment-related adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria version 5.

Statistical analysis

The index date was defined as the start date of the initial Gem/Cis/nab-P regimen for all patients, except for those in the nab-P addition without PD group. In the nab-P addition without PD group, the start date of the previous Gem/Cis-based

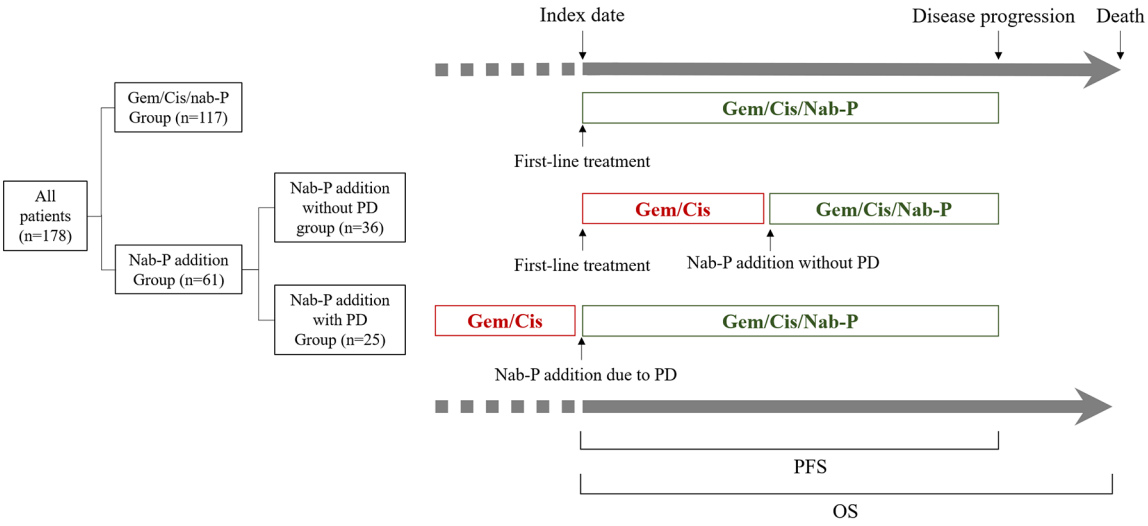

Figure 1. CONSORT diagram and study scheme.
Gem/Cis, gemcitabine-cisplatin; Gem/Cis/nab-P, nab-paclitaxel plus gemcitabine-cisplatin; nab-P, nab-paclitaxel; PD, progressive disease; PFS, progression-free survival; OS, overall survival.

regimen was regarded as the index date. PFS was defined as the time from the index date to the date of disease progression or death from any cause, whichever occurred first. OS was defined as the time from the index date to death from any cause (Figure 1). Survival outcomes were estimated using Kaplan–Meier curves and compared using a log-rank test. Statistical significance was defined as a two-sided p value <0.05. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 27.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

A total of 178 patients who received Gem/Cis/nab-P chemotherapy were included in this study. Baseline patient characteristics are summarized in Table 1. The median age was 62 years (range 33–84 years), and 110 patients (61.8%) were male. The most common primary site of the tumor was intrahepatic (43.8%), followed by extrahepatic (34.8%), and the gall bladder (21.3%). Most patients had metastatic or recurrent disease (74.7%) or had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (94.4%) at the time of Gem/Cis/nab-P treatment. The lymph node was the most common metastatic site (50.6%), followed by the liver (42.7%), lung (23.0%), and peritoneum (22.5%).

Of all the study patients, the Gem/Cis/nab-P group was the predominant with 117 (65.7%) patients, while the remaining 61 (34.3%) were in the nab-P addition group. Within the nab-P addition group, 36 patients were in the nab-P addition without PD group and 25 in the nab-P addition with PD group.

Objective responses

Complete and partial responses were achieved in 3 (1.7%) and 72 (40.4%) patients, respectively. Best responses were achieved in stable disease and PD in 76 (42.7%) and 27 (15.2%) patients, respectively. The resultant ORR and DCR were 42.1% and 84.8% in all patients (Table 2). The ORR and DCR were 47.9% and 89.7% in the Gem/Cis/nab-P group and 31.1% and 75.4% in the nab-P addition group, respectively. The ORR and DCR were 38.9% and 86.1% in the nab-P addition without PD and 16.0% and 60.0% in the nab-P addition with PD groups, respectively (Table 3). When responses were analyzed by primary tumor site, the ORR was higher in patients with extrahepatic CCA (48.4%) than in those with intrahepatic CCA (39.7%) or GBC (36.8%), but the difference was not statistically significant ($p=0.446$). When patients were stratified according to the starting dose, the ORR was 36.6% in the high-dose group and 46.2% in the reduced-dose group ($p=0.310$). A total of 20 patients (11.2%) underwent conversion from unresectable

Table 1. Baseline patient characteristics.

Characteristics	*n* = 178
Age, years, median (range)	62 (33–84)
Sex, male	110 (61.8%)
ECOG performance status	
0/1	168 (94.4%)
2	10 (5.6%)
Primary tumor site	
Intrahepatic	78 (43.8%)
Extrahepatic	62 (34.8%)
Gall bladder	38 (21.3%)
Extent of disease	
Metastatic or recurred	133 (74.7%)
Locally advanced	45 (25.3%)
Histology	
Adenocarcinoma	170 (95.5%)
Adenosquamous carcinoma	4 (2.2%)
Others	4 (2.2%)
Previous therapy	
Curative surgery	49 (27.5%)
Palliative surgery	5 (2.8%)
Adjuvant chemotherapy	25 (14.0%)
Biliary stenting	70 (39.3%)
Radiotherapy	14 (7.9%)
Palliative chemotherapy	61 (34.3%)
	GemCis: 44
	GemCis + ICI: 16
	GemCis + Paclitaxel: 1
Number of metastatic organs, median (range)	1 (0–5)
Site of metastases	
Lung	41 (23.0%)
Liver	76 (42.7%)
Lymph nodes	90 (50.6%)
Peritoneum	40 (22.5%)
Bone	17 (9.6%)
Median CA19-9, U/ml (IQR), at the time of adding nab-P	196.5 (37.7–1079.0)

GemCis, Gemcitabine-Cisplatin; nab-P, nab-paclitaxel; ECOG, Eastern Cooperative Oncology Group; CA19-9, carbohydrate antigen 19-9; ICI, immune-checkpoint inhibitor; IQR, inter-quartile range.

to resectable disease and subsequently underwent surgery. Of these 20 patients, extrahepatic CCA was the most common subtype ($n = 12$), followed by intrahepatic CCA ($n = 5$) and GBC ($n = 3$). One patient with locally advanced unresectable extrahepatic CCA showed pathologic complete response after surgery.

Survival

The median follow-up duration was 10.1 months (95% CI, 9.6–10.6). The median PFS and OS were 8.5 months (95% CI, 6.9–10.1) and 14.6 months (95% CI, 10.7–16.2), respectively (Figure 2a). In Gem/Cis/nab-P group, the median PFS was 9.4 months (95% CI, 7.9–10.9) and the median OS was not-reached (95% CI, not available) (Figure 2b). The median PFS and OS were 7.3 months (95% CI, 5.6–9.0) and 11.9 months (95% CI, 10.8–13.7) in nab-P addition group, respectively. In the nab-P addition without PD group, the median PFS and OS were 8.8 months (95% CI, 5.2–12.5) and 13.3 months (95% CI, 12.2–14.3), these were and 4.4 months (95% CI, 3.0–5.7) and 7.3 months (95% CI, 6.0–8.7) in the nab-P addition with PD group, respectively. In terms of primary tumor site, the median PFS in patients with extrahepatic CCA, intrahepatic CCA, and GBC were 11.6 months (95% CI, 9.3–13.9), 7.5 months (95% CI, 5.4–9.6), and 6.9 months (95% CI, 5.7–8.1), respectively. The median OS was 14.6 months (95% CI, 12.6–16.7), 24.4 months (95% CI, not available), and 13.3 months (95% CI, 8.3–18.2), respectively. The median PFS and OS were 4.4 months (95% CI, 3.0–5.7) and not-reached (95% CI, not available) in high-dose group, 7.8 months (95% CI, 5.7–9.8) and 14.6 months (95% CI, 12.1–17.1)

Table 2. Treatment response.

	Overall ($n=178$)	Gem/Cis/nab-P group ($n=117$)	Nab-P addition group ($n=61$)[a]	Intrahepatic ($n=78$)	Extrahepatic ($n=62$)	Gallbladder ($n=38$)
Best responses						
Complete response	3 (1.7%)	3 (2.6%)	0	0	2 (3.2%)	1 (2.6%)
Partial response	72 (40.4%)	53 (45.3%)	19 (31.1%)	31 (39.7%)	28 (45.2%)	13 (34.2%)
Stable disease	76 (42.7%)	49 (41.9%)	27 (44.3%)	31 (39.7%)	30 (48.4%)	15 (39.5%)
Progressive disease	27 (15.2%)	12 (10.3%)	15 (24.6%)	16 (20.5%)	2 (3.2%)	9 (23.7%)
ORR	42.1%	47.9%	31.1%	39.7%	48.4%	36.8%
DCR	84.8%	89.7%	75.4%	79.5%	96.8%	76.3%

[a]Best response after the addition of nab-paclitaxel.
Gem/Cis/nab-P, nab-paclitaxel plus gemcitabine-cisplatin; nab-P, nab-paclitaxel; ORR, objective response rate; DCR, disease control rate.

in reduced-dose group, respectively (Supplemental Table S1).

Safety profile

The AE profiles are listed in Table 4. The most common AEs of any grade were anemia ($n=139$; 78.1%), neutropenia ($n=127$; 71.3%), alopecia ($n=122$; 68.5%), and fatigue ($n=107$; 60.1%). Grade 3 or higher AEs occurred in 86 patients (48.3%). No treatment-related deaths occurred. Anemia was the most common AE of grade 3 or higher ($n=42$; 23.6%), followed by neutropenia ($n=40$; 22.5%). Febrile neutropenia occurred in 13 patients (7.3%). There were 88 patients (49.4%) who required dose reduction. The most common cause of dose reduction was general weakness ($n=24$), followed by neutropenia ($n=22$), sensory neuropathy ($n=8$), and fatigue ($n=6$).

Grade 3 or higher AEs occurred in 40 (56.3%) patients in the high-dose group and 46 (43.0%) patients in the reduced-dose group. Anemia at grade 3 or higher was found in 26.8% of patients in the high-dose group and 21.5% in the reduced-dose group. Moreover, neutropenia at grade 3 or higher was reported in 35.2% of patients in the high-dose group and 14.0% in the reduced-dose group. Febrile neutropenia occurred more frequently in the high-dose group than in the reduced dose group (12.7% *versus* 3.7%). A total of 38 patients (53.5%) required dose reduction in the high-dose group and 50 (46.7%) in the reduced-dose group. Five patients (2.8%) in the high-dose group discontinued Gem/Cis/nab-P because of the following AEs: decreased renal function ($n=2$), pancytopenia ($n=2$), and cholangitis ($n=1$). No patient required discontinuation in the reduced-dose group.

Table 3. Treatment response in nab-paclitaxel addition group.

	Nab-P addition without PD group[a] ($n=36$)	Nab-P addition with PD group[b] ($n=25$)
Best response after addition of nab-P		
Complete response	0	0
Partial response	14 (38.9%)	4 (16.0%)
Stable disease	17 (47.2%)	11 (44.0%)
Progressive disease	5 (13.9%)	10 (40.0%)
ORR	38.9%	16.0%
DCR	86.1%	60.0%

[a]Nab-paclitaxel (nab-P) plus gemcitabine-cisplatin (Gem/Cis) triplet chemotherapy initiated without disease progression during previous Gem/Cis (±investigational drug) treatment.
[b]Nab-P plus Gem/Cis chemotherapy initiated after progression of disease during previous Gem/Cis (±investigational drug) treatment.
PD, progressive disease; nab-P, nab-paclitaxel; ORR, objective response rate; DCR, disease control rate.

Discussion

In this study, we evaluated the real-world efficacy and toxicities of Gem/Cis/nab-P in Korean patients with advanced BTC. The 178 patients included in the present analysis showed an ORR of 42.1% and a median PFS of 8.5 months. The

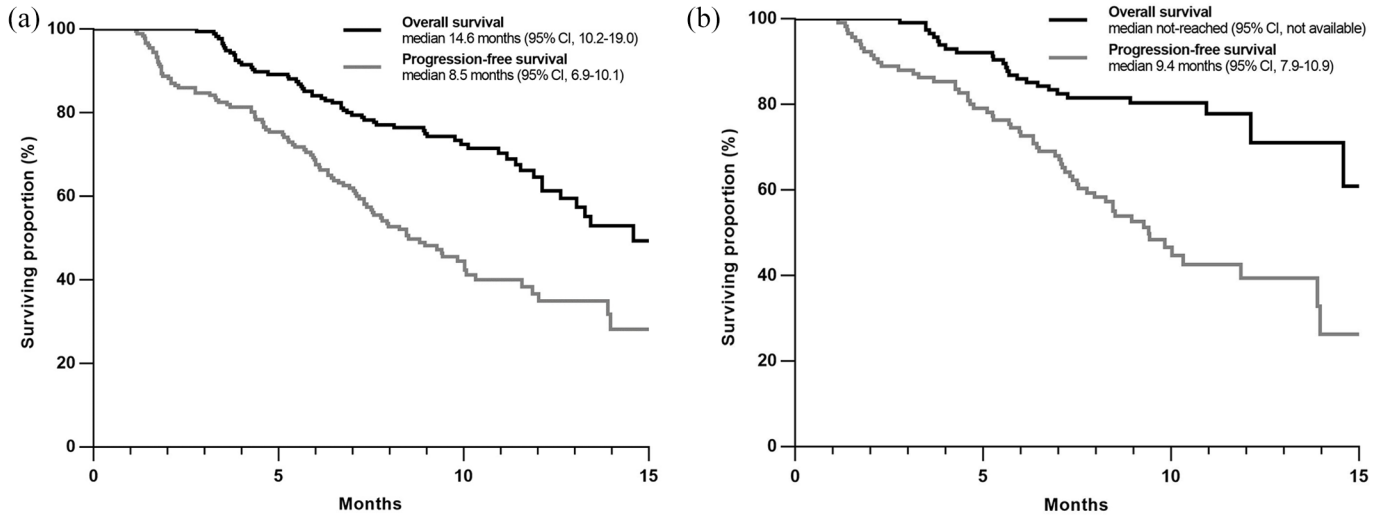

Figure 2. Progression-free survival and overall survival with all patients (a) and patients who received nab-paclitaxel plus gemcitabine-cisplatin as initial treatment (b).

patients who received Gem/Cis/nab-P as initial chemotherapy for advanced BTC showed a median PFS of 9.4 months and OS was not-reached with median follow up of 10.1 months. These survival outcomes are a promising signal compared with that seen with Gem/Cis without nab-P, which showed a median PFS of 5.2 months and a median OS of 10.4 months.[6] Although a prospective randomized trial is required to establish the efficacy of triplet regimen compared with Gem/Cis chemotherapy, our survival outcomes suggest that Gem/Cis/nab-P seems to be potent for Asian patients with advanced BTC.

One of the main differences between Gem/Cis/nab-P and Gem/Cis chemotherapy for advanced BTC is the unprecedentedly high response rate with the former. In our study, patients treated with Gem/Cis/nab-P from the beginning had an ORR of 47.9%. As previous study of 740 Korean patients who received Gem/Cis chemotherapy demonstrated ORR of 13%, our results suggest that the combination of Gem/Cis/nab-P is likely to be more effective than Gem/Cis regimen in patients with advanced BTC.[6] This promising response rate with the triplet regimen can lead to new opportunities for conversion to surgery. A total of 20 patients (11.2%) were converted from unresectable to resectable disease and underwent surgery. This is consistent with the previous phase II study which reported that 12 patients (20%) had the opportunity to undergo surgery after Gem/Cis/nab-P chemotherapy.[11] As the response rate improved after the introduction of Gem/Cis/nab-P chemotherapy, the chance of conversion to surgery increased accordingly. It is expected that a multidisciplinary approach will become more prominent in the treatment of patients with advanced BTC. Furthermore, these encouraging results of triplet chemotherapy can contribute to alleviating the chances of systemic recurrence that commonly occurs after surgery in patients with resectable BTC. Neoadjuvant studies evaluating this triplet regimen in borderline resectable intrahepatic CCA are currently being conducted in parallel in patients of different ethnicity [ClinicalTrials.gov identifiers: NCT03579771 and NCT0456828].

Gem/Cis/nab-P combination therapy showed acceptable safety profiles. There were no new safety-related events in the Asian patients in a real-world setting. This is consistent with the results of the recent phase II trial. Most AEs were well tolerated with appropriate dose modifications and appropriate supportive care. As expected, hematologic AEs [anemia (23.6%) neutropenia (22.5%), and thrombocytopenia (9.0%)] were the most common grade 3–4 toxicities. These percentages are higher than those seen with patients who received Gem/Cis therapy in the ABC-02 trial.[4] When the patients were stratified according to the initial dose of Gem/Cis/nab-P, hematologic toxicities, febrile neutropenia, and non-hematologic toxicities including diarrhea, fatigue, and sensory neuropathy at grade 3 or higher occurred more frequently in the high-dose group compared with the reduced-dose group. As

Table 4. Safety profile of nap-paclitaxel plus gemcitabine-cisplatin according to CTCAE 5.0.

AE	All (*n* = 178)		High-dose group (*n* = 71)		Reduced-dose group (*n* = 107)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any AE	177 (99.4%)	86 (48.3%)	70 (98.6%)	40 (56.3%)	107 (100%)	46 (43.0%)
Alopecia	122 (68.5%)	0	17 (23.9%)	0	105 (98.1%)	0
Anorexia	96 (53.9%)	1 (0.6%)	29 (40.8%)	1 (1.4%)	67 (62.6%)	0
Nausea	73 (41.0%)	0	14 (19.7%)	0	59 (55.1%)	0
Vomiting	19 (10.7%)	0	6 (8.5%)	0	13 (12.1%)	0
Diarrhea	21 (11.8%)	4 (2.2%)	12 (16.9%)	3 (4.2%)	9 (8.4%)	1 (0.9%)
Fatigue	107 (60.1%)	2 (1.1%)	34 (47.9%)	2 (2.8%)	73 (68.2%)	0
Sensory neuropathy	78 (43.8%)	6 (3.4%)	31 (43.7%)	6 (8.5%)	47 (43.9%)	0
Anemia	139 (78.1%)	42 (23.6%)	36 (50.7%)	19 (26.8%)	103 (96.3%)	23 (21.5%)
Thrombocytopenia	86 (48.3%)	16 (9.0%)	21 (29.6%)	9 (12.7%)	65 (60.7%)	7 (6.5%)
Neutropenia	127 (71.3%)	40 (22.5%)	51 (71.8%)	25 (35.2%)	76 (71.0%)	15 (14.0%)
ALT elevation	78 (43.8%)	4 (2.2%)	33 (46.5%)	2 (2.8%)	45 (42.1%)	2 (1.9%)
AST elevation	71 (39.9%)	3 (1.7%)	25 (35.2%)	0	46 (43.0%)	3 (2.8%)
Hyperbilirubinemia	45 (25.3%)	3 (1.7%)	18 (25.4%)	3 (4.2%)	27 (25.2%)	0
Impaired renal function	29 (16.3%)	0	5 (7.0%)	0	24 (22.4%)	0
Febrile neutropenia	–	13 (7.3%)	–	9 (12.7%)	0	4 (3.7%)
Dose reduction or interruption	88 (49.4%)		38 (53.5%)		50 (46.7%)	
Cessation	5 (2.8%)		5 (7.0%)		0	

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events.

the previous phase II trial suggested, the reduced dose of Gem/Cis/nab-P appeared to be better tolerated without significant differences in efficacy.

Our study had several limitations. First, our study was retrospective in design and, therefore, subject to unintentional bias. Second, the follow-up duration was not long enough to allow evaluation of the long-term survival of patients who received Gem/Cis/nab-P chemotherapy. Third, the patients' treatment courses were heterogeneous in terms of the starting dose, prior systemic therapy (Gem/Cis-based regimen), and timing of nab-P administration. However, the strength of this study was the inclusion of the largest reported population for Gem/Cis/nab-P therapy, which allowed the assessment of the real-world efficacy of this triplet regimen in patients with different BTC subtypes.

In conclusion, this study showed that the real-world efficacy and safety of Gem/Cis/nab-P for Asian patients with advanced BTC, in whom the incidence rate is high, were in line with the outcomes shown in the previous phase II trial.[11] It is necessary to confirm the long-term survival outcomes of patients who receive Gem/Cis/nab-P chemotherapy through a phase III trial.

Author contributions

Study concepts: JC, CL, BK and HJC. Study design: JC, CL, BK and HJC. Data acquisition: All authors. Data analysis and interpretation: All authors. Statistical analysis: JC, CL, BK, HJC.

Manuscript preparation: JC, CL, HJC. Manuscript editing: All authors. Manuscript review and approval: All authors

Conflict of interest statement

HJ.Chon has a consulting or advisory role at Roche, Bayer, Eisai, ONO, BMS, and MSD. J.Cheon received honoraria from Bayer, Eisai, Ipsen, MSD, BMS and Roche. All other authors have no potential conflicts of interest to declare.

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Statement of ethics

This study was approved by the Institutional Review Board of each participating center (CHA Bundang Medical Center, 2020-11-003; Yonsei Cancer Center, 4-2020-0771; Ulsan University Hospital, 2020-08-016; Samsung Changwon Hospital, 2021-03-001) and was performed in accordance with the ethics standards of the institutional research and the Declaration of Helsinki. The need for informed consent in this study was waived, as Korean regulations do not require consent for retrospective analyses.

Supplemental material

Supplemental material for this article is available online.

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