Original Research

Prolonged progression-free survival achieved by gemcitabine, cisplatin, and albumin-bound paclitaxel for the treatment of advanced biliary tract cancers

Jin Ho Choi*, Hwanhee Park*, Joo Kyung Park, Jong Kyun Lee,
Kyu Taek Lee and Kwang Hyuck Lee

Abstract

Background: A regimen of gemcitabine, cisplatin, and nab-paclitaxel (GPA) has shown promising results in patients with advanced biliary tract cancer (aBTC).

Objectives: This study aimed to evaluate the benefit of GPA compared to a regimen of gemcitabine plus cisplatin (GP) in patients with aBTC.

Design: Retrospective study.

Methods: Patients with aBTC who received first-line chemotherapy with GPA or GP regimen at the Samsung Medical Center between July 2020 and June 2022 were included. The primary endpoint was progression-free survival (PFS).

Results: In all, 37 patients were treated with GPA and 43 patients with GP. The GPA group showed significantly longer median PFS [12.0 months (95% CI, 7.2–16.8)] compared to the GP group [5.5 months (95% CI, 3.7–7.4; $p = 0.007$)]. The median overall survival (OS) was also longer in the GPA group [18.7 months (95% CI, 13.7–23.7)] than in the GP group [10.7 months (95% CI, 1.5–19.9); $p = 0.021$]. First-line chemotherapy with GPA was associated with longer PFS, while metastatic disease at initial diagnosis and post-treatment increase in CA 19-9 level were associated with worse PFS.

Conclusion: The GPA regimen improved the PFS of patients with aBTC compared to the GP regimen but showed no significant benefit in terms of OS after adjusting for confounding variables. Further large-scale studies are required to establish optimal indications for GPA.

Plain language summary

Comparing new and standard chemotherapy treatments for advanced biliary tract cancer: a study of effectiveness and survival

In this study, researchers at Samsung Medical Center investigated the effectiveness of two chemotherapy regimens for advanced biliary tract cancer (aBTC) from July 2020 to June 2022. The study compared a new treatment combination, gemcitabine, cisplatin, and nab-paclitaxel (GPA), against the standard treatment of gemcitabine and cisplatin (GP). The main focus was on progression-free survival (PFS) — the time patients lived without their cancer worsening, and overall survival (OS) — the total lifespan after treatment. A total of 37 patients received the GPA treatment, while 43 received the GP treatment. The results showed that patients on the GPA regimen had a longer median PFS of 12.0 months, compared to 5.5 months for those on the GP regimen. This significant difference suggested that GPA might be more effective in slowing cancer progression. Moreover, the median

Correspondence to:
Kwang Hyuck Lee
Department of Medicine,
Samsung Medical Center,
Sungkyunkwan University
School of Medicine, 81
Irwon-ro, Gangnam-gu,
Seoul 06351, Republic of
Korea
lkhyuck@gmail.com

Jin Ho Choi
Hwanhee Park
Joo Kyung Park
Jong Kyun Lee
Kyu Taek Lee
Department of Medicine,
Samsung Medical Center,
Sungkyunkwan University
School of Medicine, Seoul,
Republic of Korea

*These authors
contributed equally to this
work as the first author

OS was also longer for patients treated with GPA (18.7 months) than for those with the GP regimen (10.7 months). These findings indicated that GPA not only delayed the progression of cancer but also potentially increased the overall survival time of patients. However, when accounting for other factors that could influence the results, the advantage of GPA in terms of overall survival became less clear. This suggests that while GPA is effective in delaying disease progression, its impact on extending the overall life expectancy of patients with aBTC is not definitive. Despite these promising findings, the researchers cautioned that the benefits of the GPA regimen in extending overall survival need further investigation. The study underscores the potential of GPA in improving outcomes for aBTC patients but also highlights the necessity for more comprehensive studies. These future studies are needed to confirm the optimal treatment for this challenging cancer type. This research is a step towards better understanding and managing aBTC, a cancer that currently has limited treatment options.

Introduction

The incidence of biliary tract cancer (BTC) is increasing globally and the incidence rate in the Asian population is much higher than that in the Western population.[1,2] Based on the anatomical location, BTCs are classified as intrahepatic cholangiocarcinoma (IHCC), extrahepatic cholangiocarcinoma (EHCC), and gallbladder cancer (GBC).[3] Most patients with BTC are diagnosed at an advanced stage and, therefore, have a poor prognosis. The 5-year survival rate of patients with metastatic BTC is approximately 2%.[4,5] Systemic treatment is the standard for advanced BTC (aBTC), although these tumors show substantial resistance to systemic chemotherapy, leading to poor prognoses. Based on the ABC-02 trial, a combination of gemcitabine and cisplatin (GP) has been the standard first-line systemic therapy for aBTCs for over a decade; however, the prognosis is poor with a median overall survival (OS) of less than 1 year.[6–9] Strategies to enhance the efficacy of the standard first-line treatment for aBTC have included the exploration of novel drugs and the addition of a third agent to the GP regimen, including molecularly targeted agents and immune checkpoint inhibitors. However, these strategies have offered modest survival benefits. Therefore, development of new first-line strategies for the management of aBTC is imperative.[10–13]

To date, several clinical trials have used combination regimens, including gemcitabine-based or non-gemcitabine-based chemotherapeutic regimens, for the treatment of aBTCs.[14–18] Among them, a phase II clinical trial showed promising results of a triplet chemotherapy regimen comprising gemcitabine, cisplatin, and nab-paclitaxel (GPA) in patients with aBTC [objective response rate: 45%; median progression-free survival (PFS): 11.8 months; OS: 19.2 months].[17] However, another study showed no additional survival benefit of GPA compared to GP regimen in patients with aBTC.[19] Thus, there is a lack of robust evidence supporting the superiority of GPA over GP. Moreover, the subgroups of patients who are more likely to benefit from GPA are yet to be identified. Hence, this study aimed to evaluate the benefit of GPA regimen compared to GP regimen in patients with aBTC in a real-world setting.

Methods

Patient selection and data collection

We retrospectively analyzed patients with pathologically confirmed aBTC who received palliative chemotherapy with GPA or GP regimen at the Samsung Medical Center between July 2020 and June 2022. The exclusion criteria were as follows: (1) patients who underwent surgical resection before chemotherapy; (2) patients who had received other chemotherapy before GP or GPA; or (3) patients who were lost to follow-up with insufficient data for response evaluation.

Data were retrieved from our institution's electronic medical record. The requirement for informed consent was waived by our Institutional Review Board (IRB)/Ethics Committee due to the retrospective nature of the study and the use of de-identified patient data.

The reporting of this study conforms to the STROBE statement.[20]

Treatment and dose modification
In the GPA group, as described in the phase II trial, patients received gemcitabine (1000 mg/m^2), cisplatin (25 mg/m^2), and nab-paclitaxel (125 mg/m^2) on days 1 and 8 every 3 weeks.[17] In the GP group, patients received a standard dose of gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on days 1 and 8 every 3 weeks.[6] Initial dose reductions as well as subsequent dose modifications and interruptions to minimize adverse events (AEs) were at the discretion of the treating physicians. AEs were assessed according to the guidelines of the American Society of Clinical Oncology.[21]

Endpoints and assessment
The primary endpoint was PFS, which was defined as the time from the first day of chemotherapy until the day of either disease progression or death due to any cause. The secondary endpoints were OS, overall response rate (ORR), disease control rate (DCR), the initial level of and changes in carbohydrate antigen (CA) 19-9, and AEs. Overall response was the sum of complete response (CR) and partial response (PR), while disease control was the sum of CR, PR, and stable disease (SD). Tumor response assessments were performed every three to four cycles using CT, MRI of the chest, abdomen, and pelvis or positron emission tomography. The response was assessed by the treating physicians based on Response Evaluation Criteria in Solid Tumors, version (RECIST) 1.1.[22]

Statistical analysis
Statistical analysis was performed using Statistical Package for the Social Sciences, version 27.0.1.0 (IBM, Chicago, IL, USA). Between-group differences with respect to categorical variables were assessed for statistical significance using the chi-square test or Fisher exact test. Continuous variables were analyzed using the *t*-test (if normally distributed) or the Mann–Whitney *U* test (if non-normally distributed). Kaplan–Meier curves were used for survival analyses and between-group differences were assessed using the log-rank test. Univariable and multivariable Cox proportional-hazards regression models were used to identify the factors that significantly affected PFS and OS. The hazard ratio and corresponding 95% confidence interval (CIs) were employed to evaluate the relationship of several risk factors with PFS or OS. *p*-Values <0.05 were considered indicative of statistical significance.

Results

Study population and baseline characteristics
Of the 93 patients, 13 patients were excluded (three patients underwent operation; one had received prior chemotherapy, and nine were lost to follow-up before the first response evaluation). The remaining 80 patients were included in the analysis (Figure 1). Of the 80 patients, 37 patients were treated with the GPA regimen (GPA group) and 43 patients were treated with the GP regimen (GP group). The baseline characteristics of the study patients are summarized in Table 1. The median ages of patients in the GPA and GP group were 64.1 ± 8.6 years and 70.8 ± 7.1 years, respectively ($p < 0.001$). There were significant between-group differences with respect to the type of tumor ($p = 0.044$). GBC was more frequent in the GP group (14 of 43, 32.6%) compared to the GPA group (4 of 37, 10.8%). EHCC was more frequent in the GPA group (14 of 37, 37.8%) compared to the GP group (9 of 43, 20.9%). There were no significant between-group differences in terms of the other clinical features.

Treatment profile, response to treatment, and survival outcomes
A comparison of the treatment profile and the response in the two groups is shown in Table 1. During the follow-up period, 10 patients (27.0%) in the GPA group and 26 patients (60.5%) in the GP group had died ($p = 0.004$), while 16 patients (43.2%) in the GPA group and 35 patients (81.4%) in the GA group showed disease progression ($p < 0.001$). In terms of best response, there was no significant difference between the two groups ($p = 0.133$). The ORR was 43.2% (16 of 37 patients) in the GPA group and 27.9% (12 of 43 patients) in the GP group ($p = 0.152$); the DCR was 83.8% (31 of 37 patients) and 65.1% (28 of 43 patients), respectively ($p = 0.058$).
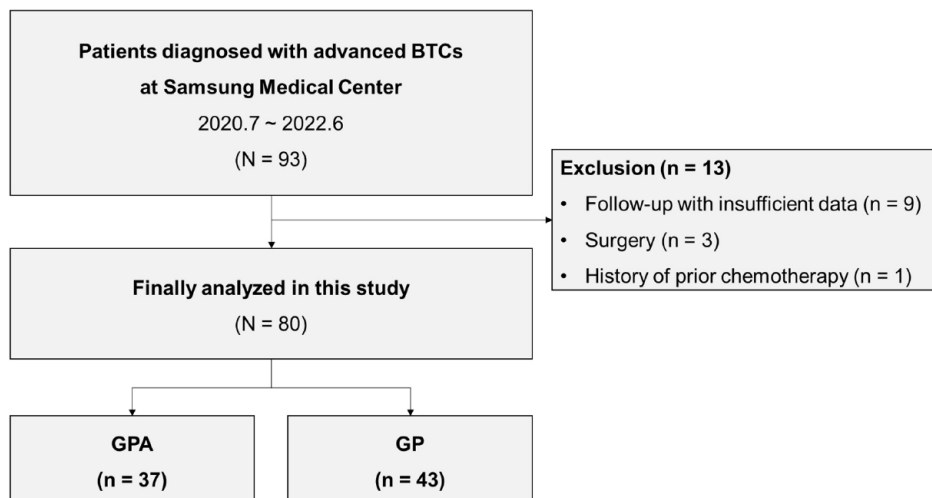
Figure 1. Flowchart of this study.

The Kaplan–Meier curves for PFS and OS are shown in Figure 2. The estimated PFS in the GPA group [median: 12.0 months (95% CI, 7.2–16.8)] was significantly longer than that in the GP group [median: 5.5 months (95% CI, 3.7–7.4); $p = 0.007$; Figure 2(a)]. The estimated OS in the GPA group [median: 18.7 months (95% CI, 13.7–23.7)] was also significantly longer than that in the GP group [median: 10.7 months (95% CI, 1.5–19.9); $p = 0.021$; Figure 2(b)].

Predictive factors for the PFS and OS
Table 2 summarizes the results of univariable and multivariable Cox regression analyses to identify predictors of survival outcomes. On multivariable Cox regression analysis, first-line chemotherapy with GPA [hazard ratio (HR): 0.38 (95% CI, 0.20–0.69), $p = 0.002$] was associated with significantly prolonged PFS after adjusting for multiple confounders, while metastatic disease at the initial diagnosis [HR 4.14, 95% CI 2.17–7.90, $p < 0.001$] and increase in CA 19-9 level after treatment [HR 2.06, 95% CI 1.08–3.91, $p = 0.028$] were both associated with worse PFS. Moreover, metastatic disease at initial diagnosis [HR: 3.38 (95% CI, 1.51–7.56), $p = 0.003$] was associated with worse OS. While the GPA group showed a longer PFS compared to the GP group, the observed increase in OS did not persist after adjusting for multiple confounders.

Subgroup analysis
Subgroup analysis was conducted to identify the subset of BTC patients who are more likely to

benefit from the GPA regimen (Figure 3). Patients with older age (≥70 years), male sex, poor performance status (≥1), EHCC, metastatic disease, lower initial level of CA 19-9, LN metastasis, and patients without liver metastasis all appeared to benefit from GPA treatment.

Adverse events
In the GPA group, the median (interquartile range) number of treatment cycles was 6 (4–12). In all, 16 patients (43.2%) remained on their starting dose throughout the follow-up period and the mean relative dose intensities (standard deviation) of gemcitabine, cisplatin, and nab-paclitaxel were 92.1 (83.1–100), 90.8 (80.0–100), and 92.9 (83.6–100), respectively.

In the GP group, the median (interquartile range) number of treatment cycles was 6 (3–9). In all, 30 patients (69.8%) remained on their starting dose throughout the follow-up period and the mean relative dose intensities (standard deviation) of gemcitabine and cisplatin were 96.4 (89.5–100) and 96.2 (89.3–100), respectively.

The demographics and AE profiles are summarized in Table 3. Grade 3 or higher AEs occurred in 27 patients (73.0%) in the GPA group and 30 patients (69.8%) in the GP group ($p = 0.756$). The most common grade 3 or higher AEs were neutropenia (56.8%), thrombocytopenia (27.0%), and anemia (21.6%) in the GPA group and anemia (30.2%), neutropenia (25.6%), and sepsis (23.3%) in the GP group. The incidence of

Table 1. Baseline characteristics of study patients and treatment responses.

Baseline characteristics	Patients, No. (%)			
	All (*N* = 80)	GPA (*N* = 37)	GP (*N* = 43)	*p*-Value
Age, mean (standard deviation), years	67.7 (8.54)	64.1 (8.69)	70.8 (7.16)	<0.001
<70	38	27	11	
≥70	42	10	32	
Sex				0.082
Male	48 (57.1)	26 (70.3)	22 (51.2)	
Female	32 (38.1)	11 (29.7)	21 (48.8)	
ECOG PS				0.639
0	32 (38.1)	16 (43.2)	16 (37.2)	
1	43 (51.2)	18 (48.6)	25 (58.1)	
2	5 (6.0)	3 (8.1)	2 (4.7)	
Tumor type				0.044
IHCC	39 (46.4)	19 (51.4)	20 (46.5)	
EHCC	23 (27.4)	14 (37.8)	9 (20.9)	
GBC	18 (21.4)	4 (10.8)	14 (32.6)	
Disease stage				0.927
Locally advanced	32 (38.1)	15 (40.5)	17 (39.5)	
Metastatic	48 (57.1)	22 (59.5)	26 (60.5)	
CA 19-9, median, U/mL (IQR)	203 (40.6–1567)	201 (40.3–1548)	295 (39.7–1639)	0.590
Death, *N* (%)	36 (45.0)	10 (27.0)	26 (60.5)	0.004
Disease progression, *N* (%)	51 (63.8)	16 (43.2)	35 (81.4)	<0.001
Treatment cycle, median (IQR)	6 (4–9)	6 (4–12)	6 (3–9)	0.370
No. of patients with remaining starting dose (%)	46 (57.5)	16 (43.2)	30 (69.8)	0.017
Best response				0.133
PR	28 (35.0)	16 (43.2)	12 (27.9)	
SD	31 (38.8)	15 (40.5)	16 (37.2)	
PD	21 (26.2)	6 (16.2)	15 (34.9)	
ORR	28 (35.0)	16 (43.2)	12 (27.9)	0.152
DCR	59 (73.8)	31 (83.8)	28 (65.1)	0.058

CA 19-9, carbohydrate antigen 19-9; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; IHCC intrahepatic cholangiocarcinoma; IQR, interquartile range; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
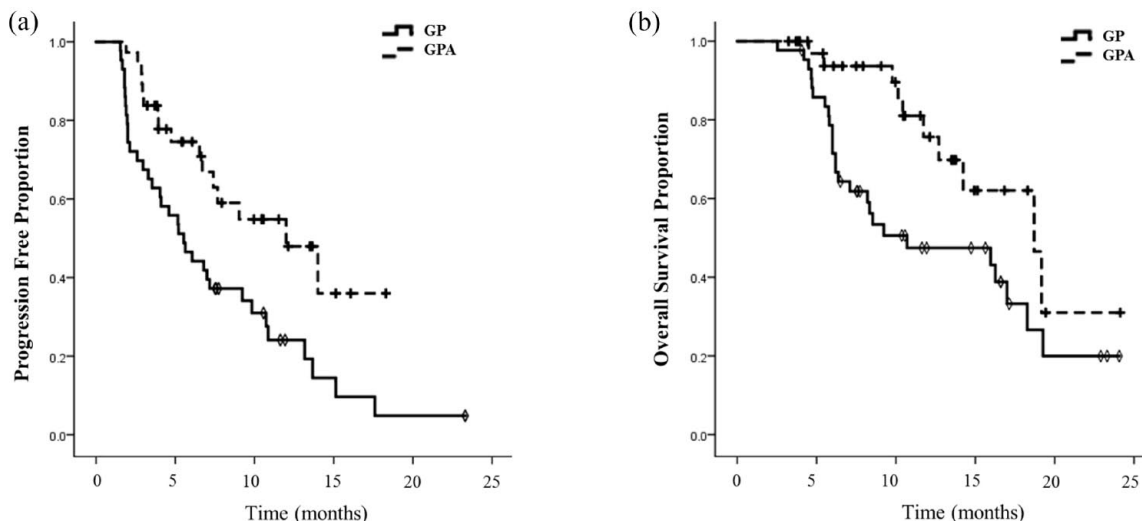
Figure 2. Kaplan–Meier curves for study patients: (a) progression-free survival and (b) overall survival.

neutropenia was significantly higher in the GPA group ($p=0.005$). The incidence of other AEs was not significantly different between the two groups.

Discussion

We compared the efficacy of GPA and GP regimens in patients with aBTC. The GPA regimen improved the survival outcomes compared to the GP regimen without an increase in severe AEs. The better PFS in the GPA group was observed even after adjusting for several other confounding factors including age. However, the GPA regimen was not found to increase OS after adjusting for other confounding factors. This is likely attributable to the fact that the metastatic BTC at initial diagnosis has the greatest impact on the OS. This finding indicates that factors beyond the first-line chemotherapy regimen itself may significantly influence the OS of patients with aBTC. These factors may include other therapeutic backups such as second-line chemotherapies, as well as conservative management strategies, such as nutritional support or appropriate control of biliary tract infection. On subgroup analysis of PFS, male patients, particularly older males, those diagnosed with metastatic EHCC, and those with a lower initial level of CA 19-9 showed better responses to the GPA regimen. However, these findings should be interpreted with caution, especially regarding the influence of age. The apparent benefit observed in older patients could potentially be a result of statistical chance, as we

currently lack a reasonable explanation for this. In addition, in our study, patients with aBTC who had LN metastasis and no liver metastasis seemed to show a better response to GPA treatment. These insights, while preliminary, are crucial for future clinical decision-making and highlight the potential for more personalized approaches for GPA therapy, allowing clinicians to select patients who are more likely to benefit from it.

The survival outcomes of GPA in our study were similar to those in the phase II trial of GPA,[17] while the survival outcomes of GP in this study were similar to those in the previous clinical trials.[6,23] In the phase II trial of GPA,[17] the OS and PFS were longer compared to the historical cohort. However, according to the abstract of the phase III trial of GPA, it did not prolong OS and PFS in aBTC when compared with GP.[24] These trials were conducted in a predominantly IHCC patient population, and approximately 70% of the patients in the recently reported phase III study had IHCC. Although the overall number of patients in the present study was small, it included a substantially higher proportion of EHCC and GBC patients. On subgroup analysis, EHCC showed a much better response to GPA, which may have affected the survival outcomes. This was consistent with the results of a recently reported multicenter retrospective study that showed an excellent DCR with GPA in EHCC when compared to other types of aBTCs.[25] However, in another single-center retrospective

Table 2. Univariable and multivariable Cox analyses of progression-free survival and overall survival.

Clinical factors	PFS				OS			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Regimen								
GP	Reference		Reference		Reference		Reference	
GPA	0.443 (0.25–0.80)	0.007	0.38 (0.20–0.69)	0.002	0.43 (0.21–0.90)	0.025	0.52 (0.22–1.23)	0.135
Age								
Age < 70	Reference				Reference		Reference	
Age ⩾ 70	1.59 (0.90–2.79)	0.108			2.55 (1.25–5.22)	0.010	1.70 (0.73–3.95)	0.215
Sex								
Male	Reference				Reference			
Female	1.76 (1.01–3.08)	0.046	1.06 (0.59–1.92)	0.839	1.02 (0.52–1.99)	0.951		
ECOG PS								
0	Reference				Reference			
1	1.28 (0.71–2.30)	0.421			1.89 (0.91–3.94)	0.089		
2	1.011(0.34–3.02)	0.984			1.53 (0.42–5.56)	0.516		
Tumor type								
IHCC	Reference				Reference			
EHCC	0.63 (0.30–1.31)	0.215			0.62 (0.25-1.55)	0.303		
GBC	1.47 (0.77–2.82)	0.241			1.45 (0.68-3.10)	0.342		
Disease stage								
Locally advanced	Reference				Reference			
Metastatic	3.729(1.99–7.00)	<0.001	4.14(2.17–7.90)	<0.001	3.31 (1.50–7.31)	0.003	3.38 (1.51–7.56)	0.003
Initial CA19-9								
<203 IU/mL	Reference				Reference			
⩾203 IU/mL	0.99(0.57–1.75)	0.995			1.094 (0.56–2.13)	0.792		
Change CA19-9								
Decreased	Reference				Reference			
Increased	2.23 (1.22–4.05)	0.009	2.06 (1.08–3.91)	0.028	0.72 (0.30–1.76)	0.471		
Dose reduction								
Done	Reference				Reference			
Not done	0.60 (0.33–1.07)	0.085			0.89 (0.45–1.75)	0.728		

CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HR, hazard ratio; IHCC intrahepatic cholangiocarcinoma.
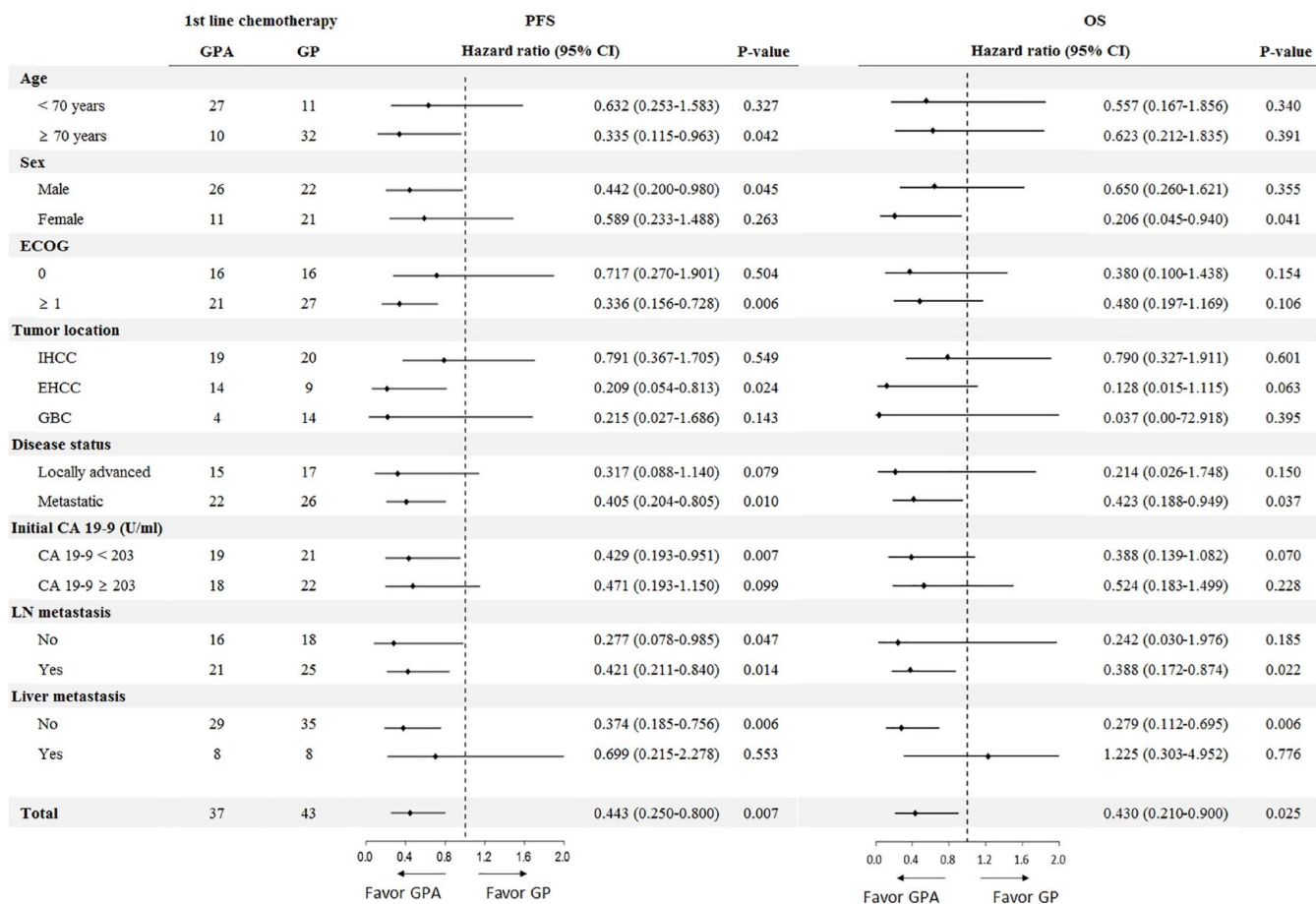
Figure 3. Forest plot for subgroup analysis of progression-free survivals in GPA and GP groups.
GPA, gemcitabine, cisplatin, and nab-paclitaxel; GP, gemcitabine plus cisplatin.

study comparing GP and GPA regimens, GPA was not found to improve the survival of patients with aBTC, thus conflicting with the results of the analysis of the predominantly EHCC patient population.[19] In that study, a historical group of patients treated with GP between 2011 and 2018 was used as a control group, and the follow-up durations were also different, which might have impacted the results. Collectively, the existing evidence suggests that it is important to consider the anatomic heterogeneity of aBTC when considering the use of GPA.

The GPA regimen showed an acceptable safety profile among patients with aBTC. Moreover, no new unexpected critical AEs were observed in this study. A relatively greater proportion of patients treated with GPA showed neutropenia but sepsis was more common in the GP group. Most patients in this study showed good tolerance to chemotherapy, with 62.2% and 74.4% of patients

in the GPA and GP groups, respectively, requiring no dose reduction. Given the safety and effectiveness of the GPA regimen in certain patient groups, we believe it is premature to dismiss GPA as a viable treatment option for aBTC. Instead, we advocate for a shift in focus toward exploring the most important predictive factors among the various tissue and molecular biomarkers that have been extensively investigated in recent research. This approach is crucial to identify patients who are most likely to benefit from GPA, thereby optimizing treatment strategies for aBTC.2,[26] An in-depth analysis of various molecular and tissue biomarkers can provide valuable insights for understanding the response to the GPA regimen in patients with aBTC.

Some limitations of our study should be considered while interpreting the results. First, this was a single-center retrospective study with an ethnically homogenous study population. Thus, our

Table 3. Comparison of adverse events between the GPA group and the GP group.

AE (grade ≥ 3)	GPA (*N* = 37)	GP (*N* = 43)	*p*-Value
Any AEs	27 (73.0)	30 (69.8)	0.756
Hematologic AEs			
Anemia	8 (21.6)	13 (30.2)	0.389
Thrombocytopenia	10 (27.0)	7 (16.3)	0.254
Neutropenia	21 (56.8)	11 (25.6)	0.005
Non-hematologic AEs			
Anorexia	0 (0)	2 (4.7)	0.160
Sepsis	3 (8.1)	10 (23.3)	0.061
Neuropathy	1 (2.7)	0 (0)	0.324
Thromboembolic event	2 (5.4)	2 (4.7)	0.879
Cr elevation	0 (0)	2 (4.7)	0.160
AST elevation	5 (13.5)	6 (14.0)	0.955
ALT elevation	5 (13.5)	2 (4.7)	0.182

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; GPA, gemcitabine, cisplatin, and nab-paclitaxel; GP, gemcitabine plus cisplatin.

findings may not be entirely generalizable to a broader, more diverse population. In addition, the relatively small sample size may have introduced an element of bias. Moreover, there were some differences between the two groups regarding patient characteristics, including age and tumor type, which could have influenced the treatment outcomes. To mitigate these limitations, we analyzed the survival outcomes in various subgroups, adjusting for several prognostic factors. However, the lack of randomization and prospective data collection might have impacted the robustness of our conclusions. Moreover, the retrospective nature of the study introduces the potential for unintentional bias, including in patient selection, data collection, and interpretation of results. Despite these limitations, our study provides real-world evidence of the promising efficacy of GPA in particular groups of patients with aBTC. Future studies with larger, more diverse populations and longer follow-up periods are required to obtain more robust evidence.

Conclusion

In conclusion, the GPA showed better PFS than the GP group, with acceptable AEs in patients with aBTC, while this was not the case for OS. The use of GPA in the appropriate patient population may help improve the prognosis of aBTC patients. Further large-scale studies will be needed to establish optimal indications of GPA in the future.

Declarations

Author contributions
Jin Ho Choi: Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Hwanhee Park: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft.

Joo Kyung Park: Methodology; Supervision; Writing – review & editing.

Jong Kyun Lee: Conceptualization; Methodology; Writing – review & editing.

Kyu Taek Lee: Methodology; Supervision; Writing – review & editing.

Kwang Hyuck Lee: Conceptualization; Methodology; Supervision; Writing – review & editing.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ORCID iD
Kwang Hyuck Lee   https://orcid.org/0000-0002-2898-6233

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