FIRST-LINE GEMCITABINE-CISPLATIN FOR ADVANCED, RECURRENT, OR METASTATIC BILIARY TRACT CANCER: TREATMENT OUTCOMES AT HANOI ONCOLOGY HOSPITAL

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ABSTRACT

Objective: To evaluate the efficacy and adverse effects of the Gemcitabine–Cisplatin regimen in patients with advanced, recurrent or metastatic biliary tract cancer at Hanoi Oncology Hospital.

Subjects and methods: A retrospective and prospective research on patients with advanced, recurrent or metastatic biliary tract cancer (including intrahepatic, extrahepatic, and gallbladder cancer) with ECOG PS 0–1, treated with at least 3 cycles of the Gemcitabine-Cisplatin regimen. The efficacy was evaluated according to RECIST 1.1 and toxicity according to CTCAE version 5.0. Survival analysis using Kaplan–Meier and Log-rank verification.

Results: Sixty-five patients were enrolled with a mean age of 56.8 ± 10.1; men accounted for 66.2%. The most common tumor site is the intrahepatic biliary tract (66.2%). The majority of patients were in the recurrent or metastasis stage (64.6%). After 3 cycles, the disease control rate reached 83.1% with an objective response rate of 29.2%. After 6 cycles, the complete response rate was 2.6%, partial response accounted for 15.8%, stable disease for 57.9% and progressed disease for 23.7%. The disease control rate reached 76.3%. The median progression-free survival was 8.1 months (95% CI: 5.4–10.7), and the median overall survival was 13.1 months (95% CI: 8.2–18.0). Performance status (ECOG, PS) and response after 3 cycles were statistically significant prognostic factors for both progression-free survival and overall survival. Common grade 3–4 adverse effects were neutropenia (38.5%), elevated liver enzymes (15.4%), and anemia (10.8%).

Conclusion: Gemcitabine - Cisplatin is an effective and acceptable safety regimen. Response and performance status after 3 cycles (ECOG PS) are important prognostic factors, which are valuable to

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Date received: 01/4/2026
Date reviewed: 10/4/2026
Date accepted for publication: 15/4/2026

guide treatment decisions. This regimen could be the first-line chemotherapy option in patients with advanced biliary tract cancer.

Keywords: biliary tract cancer; Gemcitabine; Cisplatin; chemotherapy; survival; toxicity.

1. INTRODUCTION AND STUDY OBJECTIVESS

Biliary tract cancer is a rare malignancy with a poor prognosis, often diagnosed at a late stage when the tumor has advanced or metastasized, making the possibility of radical surgery very limited. The overall 5-year survival rate for patients with advanced biliary tract cancer ranges from only 5–10%, reflecting a large burden on public health [1]. Over the past decade, many chemotherapy regimens have been studied to improve treatment outcomes for patients with advanced biliary tract cancer. The results of the ABC-02 study showed that the median overall survival (OS) time reached 11.7 months, which is higher than that of Gemcitabine alone [1]. Thus, Gemcitabine - Cisplatin is the standard treatment for advanced biliary tract cancer. Subsequent studies included TOPAZ-1 (Oh et al., 2022) and MITSUBA (Ioka et al., 2022), which continued to confirm the fundamental role of gemcitabine - cisplatin, trials with new drugs such as immunotherapy or S-1 to improve efficacy [2,4]. The Gemcitabine - Cisplatin regimen has been used in the treatment of advanced, recurrent, and metastatic biliary tract cancer at Hanoi Oncology Hospital. However, so far there have been no studies evaluating the effectiveness of this regimen. Therefore, we conducted this study with the following objectives:

- To evaluate treatment outcomes and some related factors of Gemcitabine-Cisplatin regimen on patients with advanced, recurrent, metastatic biliary tract cancer.

- To identify adverse effects of this regimen on the studied patients.

2. OBJECTS AND METHODS

2.1. Study design

The descriptive observational study combining retrospective (from January 2019 to April 2024) and prospective data (from May 2024 to September 2025).

2.2. Location and time of the study

The study was conducted at Hanoi Oncology Hospital, the time of data collection is from March 2024 to September 2025.

2.3. Sample size and sampling method

Sample size calculation formula:

$$n = z^2_{1-\alpha/2}\frac{p(1-p)}{(p\varepsilon)^2}$$

n is the minimum number of patients

p = 0.5 is the one-year survival rate of patients with biliary tract cancer. The advanced stage treated with gemcitabine-cisplatin regimens in the ABC-02 study (2010) was 39% [1].

α is the selected statistical significance level = 0.05.

z1−α/2 is the 95% confidence limiting factor, table trap = 1.96.

ε is the relative precision chosen between 0.1 - 0.4. In this study, because patients with biliary tract cancer are rare, ε = 0.117 was chosen.

Based on this formula, the calculated and actual sample size of our study was 65 patients.

Sampling method: non-random, intentional

sampling for patients with advanced biliary tract cancer with gemcitabine-cisplatin regimen that satisfied the inclusion criteria and did not violate the exclusion criteria.

2.4. Study Objects

Inclusion Criteria

- The patient was diagnosed with biliary tract cancer (including intrahepatic, extrahepatic and gallbladder biliary tract cancer) by histopathology.

- The disease was in an advanced, recurrent, or metastatic stage.

- ECOG PS 0–1.

- Treated with at least 3 cycles of the Gemcitabine–Cisplatin regimen.

- Having complete medical record and follow-up data.

Exclusion Criteria

- There are other concomitant primary cancers.

- ECOG PS > 1 or ineligibility to continue chemotherapy.

2.5. Treatment Regimen

Patients were treated with the standard Gemcitabine-Cisplatin regimen: Gemcitabine 1000 mg/m² intravenously on days 1 and 8, Cisplatin 25 mg/m² intravenously on days 1 and 8, a cycle lasted 21 days.

2.6. Efficacy and Toxicity Evaluation

- Treatment efficacy was assessed according to RECIST 1.1 by imaging tests every 2–3 cycles of chemotherapy.

- Toxicity was evaluated according to the CTCAE version 5.0.

- Progression-free survival (PFS) and overall survival (OS) were calculated from the time of initiation of chemotherapy to disease progression, death, or end of follow-up.

2.7. Data analysis

The data was processed using SPSS 20.0. Qualitative variables were represented by frequency and percentage. Survival time was analyzed using the Kaplan–Meier method and compared by Log-rank testing. The statistical significance level was determined when $p < 0.05$.

3. RESULTS

3.1. Characteristics of patients

Table 1: Characteristics of patients

Characteristic	Categories	Frequency (n=65)	Percentage
Age	Average Age (Min - Max)	56.8 ± 10.1 (22-76) years old	
Gender	Male	43	66.2
	Female	22	33.8
ECOG PS	ECOG PS 0	30	46.2
	ECOG PS 1	35	53.8
Tumor location	Intrahepatic	43	66.2
	Extrahepatic	22	33.8

Characteristic	Categories	Frequency (n=65)	Percentage
Stage	Spread in situ	12	18.5
	Progression after PT + adjuvant treatment	11	16.9
	Recurrence, metastasis	42	64.6
Biliary drainage before treatment	No	56	86.1
	Yes	9	13.9
CA19-9 before treatment	CA199 ≤ 35 U/ml	28	43.1
	CA199 > 35 U/ml	37	56.9
	Median CA199 (Min - Max)	64.5 (0.6-10500)	
Number of treatment cycles	3 cycles	16	24.6
	4 cycles	2	3.1
	5 cycles	8	12.3
	6 cycles	20	30.8
	> 6 cycles (6-14)	19	29.2
Chemo Dose	< 85%	9	13.8
	85-100%	56	86.2
Treatment Delay	No	40	61.5
	Yes	25	38.5

The Table 1 above showed that the study included 65 patients with an average age of 56.8 ± 10.1 (22–76 years), with males predominantly (66.2%). The majority of patients had ECOG PS 1 (53.8%). In terms of tumor location, intrahepatic biliary tract cancer accounted for 66.2%, extrahepatic biliary tract cancer accounted for 33.8%. The majority of patients were in the stage of recurrence and metastasis (64.6%), followed by local advanced (18.5%) and postoperative progression with adjuvant treatment (16.9%). Most patients did not need biliary drainage prior to treatment (86.1%). The median CA19-9 concentration was 64.5 UI/ml, with 56.9% of patients having CA19-9 > 35 UI/ml. In terms of treatment, the majority of patients received a full dose of chemotherapy (≥ 85%) and completed at least 6 cycles (60%), of which 61.5% did not delay treatment.

3.2. Treatment Effectiveness

3.2.1. Response Assessment

Table 2: Objective response rate (ORR)

Characteristics of response		After 3 cycles	After 6 cycles
		Number patient (%)	Number patient (%)
Controlled Disease	Complete response	2 (3.1)	1 (2.6)
	Partial response	17 (26.1)	6 (15.8)
	Stable disease	35 (53.8)	22 (57.9)
	Total	54 (83.0)	29 (76.3)
Uncontrolled Disease	Progressed disease	11 (17.0)	9 (23.7)
Total		65 (100)	38 (100)

Table 2 showed that after 3 cycles of treatment, the disease control rate reached 83.0%, in which 3.1% was complete response, 26.1% was partial response and 53.8% was stable disease; Meanwhile, 17% patients had disease progression. Among the 38 patients evaluated after 6 cycles, the disease control rate remained at 76.3%, with 2.6% patients achieved complete response, 15.8% had partial response, and 57.9% had stable disease while the rate of disease progression was 23.7%.

3.2.2. Progression free survival and overall survival

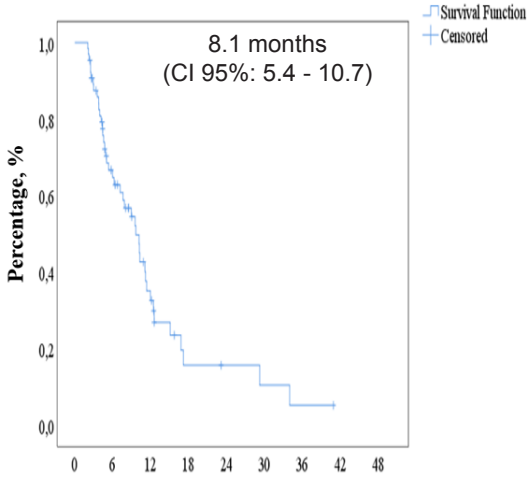

Figure 1: Kaplan–Meier curve for progression-free survival

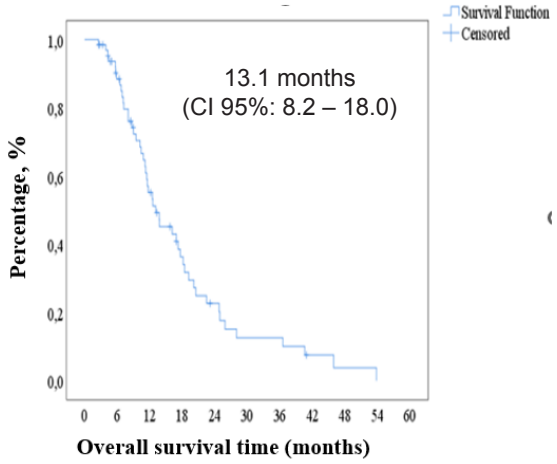

Figure 2: Kaplan–Meier curve for overall survival

The above Figure 1 illustrated the median PFS of 8.1 months (95% CI: 5.4 - 10.7). The 6-month progression-free survival rate was 61.0%, the 12-month rate decreased to 26.0%, and the 24-month rate was only 10.1%.

The Figure 2 illustrated the overall survival (OS) median of 13.1 months (95% CI: 8.2 –

18.0). The 6-month overall survival rate was 88.5%, the 12-month rate was 55.2% and %, and the 24-month rate decreased to 22.7%.

3.3. Survival and Related Factors

Table 4. Analysis relationship of survival time and factors

Factor	Frequency	Median PFS (month) (95% CI)	p (PFS)	Median OS (months) (95% CI)	p (OS)
Performance status (PS)					
PS 0	30	10.8 (4.5 - 17.1)	0.032	17.2 (9.0 - 25.4)	0.041
PS 1	35	7.9 (4.4 - 11.4)		11.6 (9.2 - 14.0)	
Biliary obstruction					
No	56	9.0 (5.5 - 12.5)	0.208	13.1 (6.8 - 19.4)	0.693
Yes	9	7.9 (0.6 - 15.2)		13.8 (10.1 - 17.5)	
Tumour location					
Intrahepatic	43	9.0 (6.3 - 11.7)	0.084	12.5 (6.2 - 18.8)	0.3
Extrahepatic	22	5.0 (2.8 - 7.2)		13.7 (11.5 - 15.9)	
Pretreatment CA19-9					
≤ 35 UI/ml	28	7.9 (5.2 - 10.6)	0.507	12.5 (4.5 - 20.5)	0.748
> 35 UI/ml	37	9.0 (6.1 - 11.9)		13.8 (11.1 - 16.5)	
Response after 3 cycles					
Response (CR+PR)	19	12.6 (11.8 - 13.4)	< 0.001	18.2 (15.5 - 20.9)	0.016
Non-response (SD+PD)	46	5.4 (3.8 - 7.0)		11.2 (9.8 - 12.6)	
Response after 6 cycles					
Response (CR+PR)	7	15.1 (9.0 - 21.2)	0.097	16.9 (0.0 - 40.8)	0.05
Non-response (SD+PD)	31	10.2 (8.6 - 11.8)		13.1 (7.8 - 18.4)	

Among the factors analyzed, ECOG PS was a statistically significant independent prognostic factor for both OS and PFS. ECOG PS 0 had a markedly longer median PFS and OS than ECOG PS 1 (10.8 vs. 7.9 months, p = 0.032; and 17.2 vs. 11.6 months, p = 0.041).

Biliary obstruction, tumor location, and pretreatment CA19-9 levels had no statistically significant association with PFS and OS (p > 0.05).

Response after 3 cycles was the most valuable prognostic factor: the responsive group (CR + PR) had a markedly superior median PFS and OS compared to the non-responsive group (12.6 versus 5.4 months, p < 0.001; and 18.2 versus 11.2 months, p = 0.016). Response after 6 cycles showed a similar, statistically significant trend for OS (p = 0.05).

3.4. Adverse effects

Table 5. Adverse effects

Adverse Effect	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)
Hepatitis	28 (43.1)	6 (9.2)	8 (12.3)	2 (3.1)	44 (67.7)
Kidney Injury	15 (23.1)	0 (0)	0 (0)	0 (0)	15 (23.1)
Anemia	36 (55.4)	10 (15.4)	7 (10.8)		53 (81.5)
Leukopenia	20 (30.8)	16 (24.6)	6 (9.2)		42 (64.6)
Neutropenia	7 (10.8)	12 (18.5)	25 (38.5)		44 (67.7)
Thrombocytopenia	22 (33.8)	11 (16.9)	8 (12.3)		41 (63.1)

Adverse effect is most common on anemia (81.5%) and neutropenia (67.7%), of which grade 3 neutropenia account for the highest proportion (38.5%). Hepatitis AE occurred in 67.7% of patients with 15.4% in grades 3-4. Neutropenia and thrombocytopenia were mainly in grades 1-2, 64.6% and 63.1%, respectively. Kidney injury was the lowest (23.1%), all at grade 1.

4. DISCUSSION

4.1. Characteristics of patients

Our study recorded the average age of populations as 56.8 ± 10.1 years, with males predominantly (66.2%). This result is similar to studies in the world, in which biliary tract cancer is common in middle to elderly age and tends to be more common in male [1,2]. The proportion of ECOG PS 1 patients accounts for 53.8%, reflecting the clinical reality in Vietnam, where the majority of patients came to the hospital at the stage when the disease has affected their physical condition. Notably, 64.6% of patients in our study were in the stage of recurrent or metastasis-a higher rate compared to another national study [5]-which partly reflects the reality of late diagnosis and limited access to curative treatment. Intrahepatic biliary tract cancer accounted for 66.2%, which is similar to the epidemiological trend of recording an increase in this disease in Asia [1]. The majority of patients did not need biliary drainage prior to treatment (86.1%), suggesting that the level of bile obstruction in the study population was not too severe, which is favorable for systemic treatment.

4.2. Treatment outcomes

Objective response rate and disease control

The disease control rate after 3 cycles in our study reached 83.1%, of which the objective response rate (ORR = CR + PR) was 29.2%. These results are similar to studies around the world, studying ABC-02 with an ORR of 26.1% [1] and TOPAZ-1 with an ORR of 26.7% [3]. Compared to the domestic study by Ninh Thi Thao (2021), the ORR in our study was lower, this difference can be explained by the significantly higher proportion of patients in the recurrent and metastatic stages in our study (64.6%), resulting in a study population with a poorer prognosis [5]. After 6 cycles, the disease control rate remained at 76.3% on 38 patients, indicating that the Gemcitabine-Cisplatin regimen has the ability to control the disease sustainably during treatment.

4.3. Progression-free survival

The median PFS in our study reached 8.1 months (95% CI: 5.4–10.7), which is equivalent to the results of the ABC-02 trial (8.0 months)

[1] and the study by Ioka et al. (2022) [4]. The 6-month progression-free survival rate reached 61.0%, decreasing to 26.0% after 12 months, reflecting the natural progression of this disease. Analysis of prognostic factors showed that ECOG PS 0 and response after 3 cycles were two statistically significant factors influencing PFS ($p = 0.032$ and $p < 0.001$). Meanwhile, bile obstruction, tumor location, and CA19-9 level did not significantly associate with PFS in this study, which is similar to some studies around the world [2,4].

4.4. Overall survival

The median OS was 13.1 months (95% CI: 8.2–18.0), which is higher than that of the majority of world studies on the Gemcitabine-Cisplatin regimen, ranging from 11.7 to 14.2 months [1, 3], although the percentage of patients with distant metastases in our study was quite high (64.6%). The 12-month overall survival rate reached 55.2%, decreasing to 22.7% after 24 months. Similar to PFS, ECOG PS 0 and response after 3 cycles continued to be statistically significant OS prognostic factors ($p = 0.041$ and $p = 0.016$), while response after 6 cycles tended to improve OS but did not reach a clear statistically significant threshold ($p = 0.05$). It may be because the sample size at this assessment time was limited. These results reinforce the role of early response as an important prognostic marker and underscore the clinical significance of assessing response after 3 cycles in the guidelines for subsequent treatment decisions.

4.5. Adverse Effects

The Gemcitabine-Cisplatin regimen in our study had a notable rate of hematotoxicity, with grade 3 neutropenia being the most common severe adverse effects (38.5%), which was higher than reported from ABC-02 and TOPAZ-1 [1,3]. Anemia occurred in 81.5% of patients but was predominantly at grades 1–2 (70.8%), without compromising regimen adherence. Hepatotoxicity which was elevated transaminase accounted for 15.4%, and should be closely monitored, especially in patients with underlying liver disease. In contrast, nephrotoxicity was very low, all at grade 1 (23.1%), no cases of renal failure of grade 2 or higher were recorded, indicating that active rehydration with cisplatin was well implemented. Higher grades of adverse effects compared to some international trials may be related to the more severe patient characteristics in the study population, however the proportion of patients who maintained the dose of ≥85% still reached 86.2% and the rate of no delay of treatment was 61.5%, indicating that adverse effects had been effectively managed in clinical practice.

5.6. Limitations of the study

We are aware of certain limitations in this study when analyzing the results. Retrospective data, limited sample size ($n = 65$), and single-center study site can affect the ability to extrapolate results. In addition, heterogeneity in disease stage in the study population-including local, recurrent, and distant metastases-should be remembered when compared to randomized controlled clinical trials. Prospective studies with larger sample sizes and clearer stratification are needed to confirm the prognostic factors identified in this study.

6. CONCLUSIONS AND LIMITATIONS OF THE STUDY

The Gemcitabine–Cisplatin regimen demonstrated clinically meaningful efficacy and an acceptable safety profile as first-line chemotherapy for patients with advanced, recurrent, or metastatic biliary tract cancer. Regarding treatment efficacy, the regimen achieved a disease control rate of 83.1% after three cycles and 76.3% after six cycles. The median progression-free survival was 8.1 months, and the median overall survival

was 13.1 months. These outcomes are comparable to those reported in major international studies and support the applicability of this regimen in real-world clinical practice at Hanoi Oncology Hospital.Regarding prognostic factors, ECOG performance status and treatment response after three cycles were significantly associated with both progression-free survival and overall survival. These findings suggest that early response assessment and baseline performance status may be useful for guiding subsequent treatment decisions. Regarding safety, hematologic toxicity was the most common adverse event, particularly neutropenia and anemia. However, most adverse events were manageable, and the majority of patients were able to maintain adequate treatment intensity. Renal toxicity was mild, with no grade 2 or higher nephrotoxicity recorded.

This study has several limitations, including its single-center design, limited sample size, retrospective–prospective nature, heterogeneous study population, and absence of multivariate analysis. Further prospective multicenter studies with larger sample sizes are needed to confirm the efficacy, safety, and independent prognostic factors of the Gemcitabine–Cisplatin regimen in Vietnamese patients with biliary tract cancer.

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