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Original Article

Adjuvant Gemcitabine-cisplatin Combination for Biliary Tract Cancer: A Real Life Experience

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ABSTRACT

Aim: Biliary tract cancers (BTCs), including gallbladder and cholangiocarcinomas, are aggressive malignancies with poor long-term survival despite surgical resection. The efficacy of adjuvant therapy in BTCs remains controversial, particularly in the absence of consistent phase 3 data supporting its survival benefit.

Methods: We conducted a retrospective, single-center study including 49 patients who underwent surgery for BTC and received adjuvant chemotherapy between 2013 and 2022. Patients with stage 1 disease, neoadjuvant treatment, unresectable/metastatic disease, or missing pathology were excluded. Survival outcomes were analyzed using Kaplan-Meier and Cox regression methods.

Results: The median overall survival (mOS) for the entire cohort was 44.8 months. The gemcitabine-cisplatin (GemCis) group had significantly longer mOS (71.5 months) than patients receiving other regimens (41.8 months; p=0.033). Advanced T stage, lymph node involvement, and tumor, node, metastasis stage 3 were associated with poorer survival. In multivariate analysis, treatment other than GemCis [hazard ratio (HR): 2.38; p=0.040] and stage 3 disease (HR: 3.32; p<0.01) were independent risk factors for decreased mOS.

Conclusion: Our findings suggest that the gemcitabine-cisplatin combination may confer a survival advantage in selected patients with BTCs, especially younger individuals with good performance status. These results support further investigation in randomized controlled trials to clarify the role of gemcitabine-cisplatin in the adjuvant setting.

Keywords: Biliary tract cancer, adjuvant chemotherapy, gemcitabine-cisplatin combination, capecitabine, cholangiocarcinoma

Introduction

Biliary tract cancers (BTCs) refers to cancers that develop in the gallbladder or the biliary epithelium of the intra-and extrahepatic bile ducts [1]. The incidence of gallbladder cancer in women is declining, while the incidence of intrahepatic cholangiocarcinoma is increasing, and extrahepatic cholangiocarcinoma remains stable [2,3]. The 5-year survival rate for patients with cholangiocarcinoma is approximately 20% [4]. Despite an increase in the early-stage diagnosis of gallbladder cancer, the 5-year survival rate for patients with advanced-stage gallbladder cancer and cholangiocarcinoma is less than 5% [5].

Surgery represents the only curative treatment option for BTCs; however, even after achieving R0 resection, the recurrence rates remain relatively high. In a study where patients were followed up after resection, 48.8% died from malignancy and 11.3% died from non-malignant causes within 28 months [6].

The effectiveness of adjuvant therapy in treating BTCs is still a subject of ongoing debate, especially with the emergence of immune checkpoint inhibitors as adjuvant treatment options

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in various cancer types [7-9]. Apart from the BTC cancer capecitabine trial (BILCAP) study, no phase 3 study has provided evidence demonstrating that adjuvant therapy is superior to a placebo [10]. Additionally, two phase 3 studies have shown that treatments containing gemcitabine did not significantly improve outcomes compared to a placebo [11,12]. The occurrence of distant recurrences, particularly in gallbladder cancers, emphasizes the need for effective adjuvant treatments [13]. In contrast to phase 3 studies, several retrospective studies have indicated that adjuvant chemotherapy agents and adjuvant chemoradiotherapy can enhance survival outcomes [14,15]. One meta-analysis of gallbladder cancers and two separate meta-analyses of cholangiocarcinomas have demonstrated that adjuvant chemotherapy improves overall survival (OS) [16-18]. However, there is a lack of phase 3 studies directly comparing different chemotherapy regimens.

The phase 2 STAMP trial compared gemcitabine-cisplatin (GemCis) and capecitabine in patients with resected, lymph node-positive extrahepatic cholangiocarcinoma and found similar median OS (mOS) in both arms (around 35.7 months), with no significant difference [hazard ratio (HR) ≈ 1.08, p=0.40] [19]. A phase 3 study (ACTICCA-1), comparing 8 cycles of GemCis with 6 months of capecitabine in resected BTCs, has been conducted, and the final results are currently awaited. This trial is expected to clarify whether GemCis offers any advantage over capecitabine in the adjuvant setting [20]. Despite its proven benefit in advanced disease, GemCis does not appear to be clearly superior to fluoropyrimidine monotherapy in the adjuvant setting. The ongoing challenge of distant recurrence, particularly in gallbladder cancer, underscores the urgent need for more effective systemic adjuvant treatments.

The objective of our study was to analyze the mOS and assess the efficacy of various chemotherapy regimens in patients with BTCs who received adjuvant chemotherapy.

Methods

Our study is a retrospective, single-center investigation that included patients aged 18 and above who underwent surgery for gallbladder cancer or cholangiocarcinoma, and received adjuvant treatment at a university cancer institute between 2013 and 2022. Patients who received neoadjuvant therapy, were at stage 1, had metastatic-unresectable tumors, or for whom pathology data could not be obtained were excluded from the study.

We collected baseline patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status, tumor pathology information, details of the treatment agents used, as well as baseline hemoglobin and albumin levels. Additionally, survival data were collected. Anemia was defined as a hemoglobin level below 12 g/dL, and hypoalbuminemia was defined as an albumin level below 3.5 g/dL.

The selection of adjuvant chemotherapy regimens was based on the treating physician's clinical judgment, taking into account factors such as patient age, performance status, and comorbidities.

All procedures involving human participants in this study adhered to the ethical standards set by the institutional and/or national research committee, as well as the guidelines outlined in the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards. Approval was obtained from the Hacettepe University Ethics Committee for the study (decision no: 2022/15-54, date: 04.10.2022).

Statistical Analysis

Where appropriate, baseline characteristics were presented as percentages, means, and standard deviations. The chi-square test was employed to assess the baseline patient characteristics of the GemCis group and the other treatment group. Survival analyses were conducted using the Kaplan-Meier method and Cox regression analyses. A p value less than 0.05 was considered statistically significant. The multivariate Cox regression analysis included parameters with p-values below 0.05. For these analyses, the Statistical Package for Social Sciences (SPSS, IBM, New York, USA) version 22 was utilized.

Results

In our study, 49 patients were involved. The patients' mean age was 59.29±11.77 years. Thirty-one patients were male, and all patients had an ECOG of 0 or 1. There were 18 patients with gallbladder cancer and 31 with bile duct cancers. The tumor stage was 2 in 24 patients, and the lymph node stage was 0 in 29 patients. Negative surgical margins were found in 41 patients, while positive microscopic surgical margins were found in 8 patients. The most commonly used treatments were GemCis combinations and capecitabine. Adjuvant radiotherapy was administered to 19 patients, while no radiotherapy was administered to the remaining 30 patients. Anemia and hypoalbuminemia appeared in 19 and 17 of the patients, respectively. Table 1 presents the demographic, pathological, and clinical characteristics of the patients.

Thirty patients died during their follow-up. mOS was 44.8±7.32 months [95% confidence interval (CI): 30.47-59.19]. Kaplan-Meier analysis was used to examine the factors that influence survival. Women had an mOS of 54.76±5.48 months (95% CI: 44.00-65.52), and men had an mOS of 36.3±4.43 months (95% CI: 27.63-45.03) (p=0.132). mOS times were found to be comparable in patients aged ≥65 (43.5±1.74 months, 95% CI: 40.08-46.91) and patients aged <65 (44.8±12.89 months, 95% CI: 19.56-70.10), with a p value of 0.324). The mOS for gallbladder cancer is 42.2±2.01 months (95% CI: 38.31-46.22), while for bile duct cancers, it is 54.7±19.63 months (95% CI: 16.28-93.24) (p=0.803). The mOS time was found to be lower as the T stage increased 71.5 months (95% CI: 55.31-87.74), 36.3 months (95% CI: 22.08-50.58), 35.5 months (95% CI: 16.45-54.54), respectively; T2, T3, and T4, p=0.024). Those who did not have lymph node metastases had a longer mOS than those who did 61.9 months (95% CI: 34.35-89.45) and 26.6 months (95% CI: 10.09-43.23), respectively; p=0.013).

Tumor, node, metastasis (TNM) stage 2 patients had a longer mOS than TNM stage 3 patients 71.5±30.18 months (95% CI: 12.317-130.69) and 35.5±5.95 months (95% CI: 23.82-47.17); p=0.002.

When compared to other treatments, patients receiving the GemCis combination had a longer mOS 71.5±33.62 months (95% CI: 5.63-137.43) and 41.8±4.07 months (95% CI: 33.84-49.82); p=0.033. The relationship between treatment regimen and mOS is shown in Figure 1.

Positive surgical margins, adjuvant radiotherapy, anemia, hypoalbuminemia, and mOS had no correlation (p=0.869, p=0.208, p=0.738, and p=0.699).

Table 1. Baseline clinical and laboratory features of patients

		No	%
Age (mean ± standard deviation)	59.29±11.77		
Age	>65	13	26.5
	<65	36	73.5
Sex	Female	18	36.7
	Male	31	63.3
ECOG score	0	47	95.9
	1	2	4.1
Tumor localization	Gallbladder cancer	18	36.7
	Intrahepatic cholangiocarcinoma	13	26.6
	Extrahepatic cholangiocarcinoma	18	36.7
Primary tumour classification	2	24	49
	3	22	44.9
	4	3	6.1
Lymph node status	0	29	59.2
	1	15	30.6
	2	5	10.2
Pathological tumour stage	2	23	44.9
	3	26	55.1
Resection margin	R0	41	83.7
	R1	8	16.3
Chemoterapy regimen	Gemcitabine plus cisplatin	26	53.3
	Gemcitabine plus fluoropyrimidine	5	10.2
	Gemcitabine	7	14.2
	Capecitabine	11	22.3
Adjuvant radiotherapy	Present	19	38.8
	Absent	30	61.2
Anemia	Present	19	38.8
	Absent	30	61.2
Hipoalbuminemia	Present	17	34.7
	Absent	32	65.3

ECOG: Eastern Cooperative Oncology Group

The parameters associated with survival in univariate analysis were included in the multivariate Cox regression analysis (T stage, N stage, TNM stage, and treatment agents). The GemCis combination treatment (HR: 2.38, 95% CI: 1.042-5.466; p=0.040) and presence of stage 3 disease (HR: 3.32, 95% CI: 1.491-7.402) were independent risk factors for mOS. Univariate and multivariate analysis results are shown in Table 2. It was found that younger patients were given the GemCis combination, whereas adjuvant radiotherapy was used more frequently in patients who received other chemotherapy. Table 3 compares the demographic, clinical, and pathological characteristics of patients receiving GemCis treatment with those receiving other therapies.

Discussion

In our retrospective study, being diagnosed at an advanced stage and receiving treatment other than GemCis were identified as independent risk factors.

BTCs encompass various components, including gallbladder, intrahepatic bile duct, and extrahepatic bile duct cancers. Due to their rarity, they are evaluated in clinical studies [10-12]. The BILCAP study compared adjuvant capecitabine treatment to observation alone. The mOS was reported as 51 months in the capecitabine arm and 36 months in the observation arm [21]. This study indicated a greater contribution of adjuvant treatment in stage 2 tumors, compared to other stages. The lower survival time observed in our study, in comparison to the BILCAP study, can be attributed to the exclusion of stage 1 patients from our analysis. The lack of statistically significant recurrence-free survival (RFS) analysis after 24 months in the BILCAP study underscores the need for alternative treatments to capecitabine. In our study, the mOS in the capecitabine arm was determined as 42.26 months (95% CI: 29.18-55.34). The lower survival time compared to the BILCAP study was due to the exclusion of stage 1 patients in our study. It is noteworthy that although capecitabine is the preferred option, the National Comprehensive Cancer Network guidelines continue to recommend a gemcitabine-based chemotherapy regimen [22].

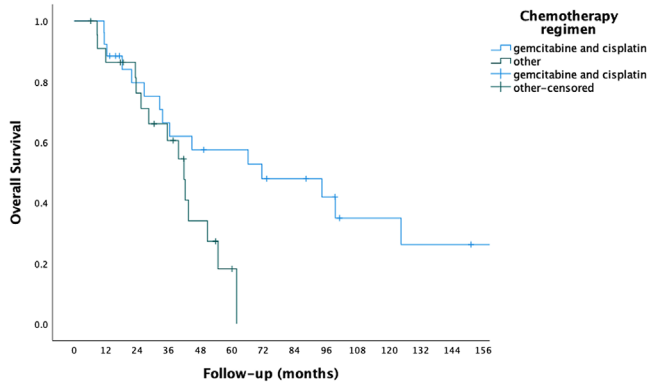

Figure 1. Overall survival according to adjuvant chemotherapy regimen

Single-agent gemcitabine therapy or combination regimens containing gemcitabine have been explored in the treatment of BTCs, drawing from the successful results seen in pancreatic cancer [23,24]. However, a study comparing adjuvant gemcitabine treatment to observation alone failed to demonstrate a survival benefit, as both arms exhibited a 60-month survival rate [12]. In the PRODIGE 12-ACCORD 18 study, the administration of adjuvant gemcitabine-oxaliplatin prolonged the mOS, but the difference was not statistically significant [11]. A meta-analysis that included the PRODIGE 12-ACCORD 18 study and the BCAT study also failed to demonstrate the contribution of gemcitabine-based adjuvant therapy [25]. The mOS in the gemcitabine arm was reported as 75 months, while it was approximately 50 months in the follow-up arm. In our study, the mOS was 43.5 months when gemcitabine was administered alone and 34.5 months when gemcitabine was combined with capecitabine.

Table 2. Univariate and multivariate analysis of factors associated with median overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% confidence interval	p	HR	95% confidence interval	p
T status (2 vs. 3-4)	2.827	1.298-6.159	0.009	2.062	0.312-13.639	0.441
N status (negative vs. positive)	2.467	1.184-5.141	0.016	1.567	0.571-4.304	0.383
Treatment (G+C vs. other)	2.395	1.050-5.462	0.038	2.386	1.042-5.466	**0.040**
TNM stage (2 vs. 3)	3.333	1.497-7.420	0.002	3.322	1.491-7.402	**0.003**

TNM: Tumor, node, metastasis, HR: Hazard ratio

Table 3. Baseline clinical and laboratory features of patients according to treatment

		Gemcitabine plus cisplatin	Others	p value
Mean age		55.27±9.76	63.84±12.38	
Age	>65	3 (11.5%)	10 (43.5%)	**0.021**
	<65	23 (88.5%)	13 (56.5%)	
Sex	Female	8 (30.8%)	10 (43.5%)	0.390
	Male	18 (69.2%)	13 (56.5%)	
ECOG score	0	25 (96.2%)	22 (95.7%)	1.00
	1	1 (3.8%)	1 (4.3%)	
Tumor localization	Gallbladder	7 (26.9%)	11 (47.8%)	0.239
	Intrahepatic	9 (34.6%)	4 (17.4%)	
	Extrahepatic	10 (38.5%)	8 (34.8%)	
Tumor stage	2	14 (53.8%)	10 (43.5%)	0.664
	3	11 (42.3%)	11 (47.8%)	
	4	1 (3.8%)	2 (8.7%)	
Lymph node stage	0	14 (52%)	15 (65.2%)	0.422
	1	10 (40%)	5 (21.7%)	
	2	2 (8%)	3 (13%)	
TNM stage	2	12 (46.2%)	10 (43.5%)	1.00
	3	14 (53.8%)	13 (56.5%)	
Resection margin	R0	21 (80.8%)	20 (87.0%)	0.706
	R1	5 (19.2%)	3 (13.0%)	
Radiotherapy	Present	4 (15.4%)	15 (65.2%)	**<0.001**
	Absent	22 (84.6%)	8 (34.8%)	
Anemia	Present	8 (30.8%)	12 (52.2%)	0.155
	Absent	18 (69.2%)	11 (47.8%)	
Hipoalbuminemia	Present	7 (28%)	10 (43.5%)	0.247
	Absent	19 (72%)	13 (56.5%)	

ECOG: Eastern Cooperative Oncology Group, TNM: Tumor, node, metastasis

Following the identification of a survival benefit with the GemCis combination, it has become the standard treatment for metastatic BTCs [26,27]. Building on its efficacy in advanced disease, studies have been conducted to evaluate its effectiveness in earlier stages. The STAMP study compared the GemCis combination with capecitabine treatment in extrahepatic bile duct cancers and found no significant difference in mOS, with both arms exhibiting an mOS of approximately 35 months [28]. In contrast to this study, real-life data have demonstrated the efficacy of the GemCis combination [25]. In our study, patients with BTC who received the GemCis combination had a remarkable mOS of 71 months. These patients were on average eight years younger, had a lower incidence of anemia, and represented a more select group. The ACTICCA-1 study, which compares adjuvant GemCis combination with capecitabine treatment in BTCs, has the potential to impact the standard treatment approach [20]. Based on our study findings, the GemCis combination yielded impressive results.

Although the OS curves for the two treatment groups were similar in the early follow-up period, a notable divergence emerged after approximately 36 months. Specifically, patients in the GemCis group showed better long-term survival, while survival rates in the other treatment group declined more rapidly. This pattern suggests that the benefit of GemCis may become more evident in the mid-to-late follow-up period, rather than in the early post-treatment phase. Therefore, the time-dependent nature of the treatment effect should be considered when interpreting the survival outcomes.

Study Limitations

We acknowledge that our study has certain limitations. Being retrospective and conducted in a single center, the patient groups may not be homogeneous, and the sample size may be insufficient. The administration of GemCis treatment to a relatively younger group of patients with better overall health may introduce bias when comparing different treatment options. Additionally, the small patient population in our study results from the inclusion of only those patients who underwent surgery at our center and subsequently received treatment and follow-up. Another important limitation of our study is the lack of RFS data for most patients, which prevented us from performing a meaningful RFS analysis. These limitations should be taken into consideration when interpreting the results of our study.

Conclusion

While capecitabine is currently considered the standard treatment for operated BTCs, our study revealed impressive results with a mOS of 71 months in young patients who were in good general condition, and received the GemCis combination. Additionally, the observed late divergence in survival curves suggests a time-dependent treatment effect, which may not be fully captured by conventional statistical methods such as the log-rank test.

These findings suggest that the GemCis combination may be a potential candidate for treatment if supported by prospective randomized controlled trials. Further research and validation through rigorous clinical trials are necessary to establish the efficacy and safety of this treatment approach in a larger patient population.

Ethics

Ethics Committee Approval: Approval was obtained from the Hacettepe University Ethics Committee for the study (decision no: 2022/15-54, date: 04.10.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.K., H.Ç.Y., A.A., Ö.D.T., B.K., D.C.G., Ö.D., Ş.Y., Concept: F.K., Ö.D., Ş.Y., Design: F.K., Ö.D., Ş.Y., Data Collection or Processing: F.K., A.Ö., F.Ş., F.B., Analysis or Interpretation: F.K., H.Ç.Y., A.A., Ö.D.T., F.Ş., B.K., D.C.G., Literature Search: F.K., Writing: F.K.

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