Original Article

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First-line systemic therapy and sequencing options in advanced biliary tract cancer: A systematic review and network meta-analysis

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SUMMARY The current state of systemic therapy for advanced biliary tract cancer (BTC) has undergone significant changes. Currently, there are no clinical trials directly comparing various first-line systemic therapy regimens to each other, and these trials are unlikely to be conducted in the future. In this systematic review, after various abstracts and full-text articles published from the establishment of the database until October 2024 were searched, we included and analysed phase 3 clinical trials to evaluate the efficacy of different first-line systemic treatment regimens in advanced BTC. We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines and a random effects model to pool the overall effects. Finally, seven low-risk-of-bias trials (with all of the trials representing first-line trials) were included. A total of 4033 patients were included in seven first-line trials. In terms of progression-free survival (PFS), network meta-analysis revealed that durvalumab + gemcitabine + cisplatin (GemCis) triple therapy, S-1 + GemCis triple therapy, and pembrolizumab + GemCis triple therapy were superior to GemCis. In terms of overall survival (OS), network meta-analysis revealed that durvalumab + GemCis triple therapy and pembrolizumab + GemCis triple therapy outperformed GemCis. According to the ranking of the P scores, durvalumab + GemCis triple therapy ranked first in PFS and second in OS. Therefore, the advantages of molecular immunotherapy have gradually become known, which suggests that future trials should focus on other potential combinations and molecular immunotargeted therapies.

Keywords cholangiocarcinoma; chemotherapy; immunotherapy; durvalumab; P-score

1. Introduction

Biliary tract carcinoma (BTC) is a rare malignant tumour with a dismal prognosis (*1*). Most cases are identified at an advanced stage, and surgical removal is not an option for treatment (*2*). For advanced BTC, chemotherapy is the first-line treatment. Immune checkpoint inhibitors (ICIs) and molecular-targeted treatment have become viable options for systemic therapy for advanced BTC as a result of the advancement of molecular-targeted therapy technologies driven by next-generation sequencing (NGS) (*3*). Additionally, systemic therapy can be used in conjunction with local therapy, such as radioembolization (*4*), hepatic arterial infusion (HAI) of chemotherapy (*5*), and transarterial (chemo) embolization (*6*). Patients with unresectable BTC have a median overall survival (OS) of approximately one year, and the 5-year survival rate is less than 10% (*7,8*).

In the previous decade, doublet chemotherapy with gemcitabine and cisplatin (GemCis) was thought to be the most successful first-line treatment of this condition(*9,10*). Treatment choices will become limited as the illness progresses, and fluorouracil-based combination therapy has demonstrated only moderate effectiveness (*11,12*). More alternatives for second-line BTC treatment are now available due to the increased focus given to personalized precision treatment based on gene and molecular targeted detection methods. According to research performed in second-line or later settings, patients with cancers that have certain molecular abnormalities, such as fibroblast growth factor receptor (FGFR)-2 fusions (*13,14*) and isocitrate dehydrogenase (IDH)-1 mutations (*15,16*),

may benefit from ICIs or targeted therapies. However, unique molecular subpopulations are uncommon, and chemotherapy is the only available therapeutic choice for the majority of individuals (*17*).

As research has progressed, GemCis is no longer the only option for first-line systemic treatment of advanced BTC. Many regimens are just as effective as GemCis, including capecitabine + oxaliplatin (XELOX) combination therapy (*18*), S-1 + gemcitabine combination therapy (*19*), pembrolizumab + GemCis triple therapy (*20*), durvalumab + GemCis triple therapy (*21*), S-1 + GemCis triple therapy (*22*), and nab-paclitaxel + GemCis triple therapy (*23*). Both durvalumab and pembrolizumab are immune agents; however, the tumour microenvironment of most BTCs is characterized by immunosuppression or immune rejection(*24*), thus resulting in a relatively low response to immunotherapy alone in advanced BTCs (*25,26*). The triple immunization regimen against advanced BTC has demonstrated better results, which may be due to the regulation of the immune system by GemCis *via* a direct immune stimulation mechanism, which downregulates the immunosuppressive microenvironment and increases immunogenicity (*27,28*).

However, until now, there have been no clinical trials comparing various first-line systemic treatment options, and no conclusive data have demonstrated which option is preferred. A network meta-analysis (NMA) is useful for comparing different drugs across randomized clinical trials (RCTs) because these studies demonstrate varying efficacy across lines of therapy (*29,30*). This scenario is particularly crucial because the recommendations that are currently in place only list the available therapies without addressing which therapies should be prioritized. In this systematic review and network meta-analysis, we ranked the effectiveness of several first-line systemic treatments (which must be indirectly compared with GemCis) in the treatment of advanced BTC.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard was followed in the reporting of this systematic review (*31*). Due to the fact that this was not a meta-analysis of individual patients, the informed consent requirements were not met, and institutional review board permission was not needed.

2.1. Study objective

The objective of the current study was to evaluate the effectiveness of several first-line systemic therapy regimens (wherein GemCis is a necessary component) in patients with advanced BTC.

2.2. Eligibility Criteria

Phase 3 randomized clinical trials for first-line systemic treatment of advanced BTC malignancies were included in the analysis (with the regimens including GemCis).

2.3. Data Sources and Search Strategies

An extensive search of the literature was performed in the PubMed and Web of Science databases for abstracts and full-text articles that fit the criteria. PFS and OS for all of the patients receiving first-line therapy represented the outcomes of interest.

2.4. Study Selection

Relevant abstracts and full-text papers were identified *via* the title list, and these abstracts and papers were subsequently examined.

2.5. Data Extraction

Prespecified data, such as sample sizes, baseline characteristics, and utilized therapies, were extracted from each study *via* a standardized data abstraction form.

2.6. Risk of Bias and Certainty of Evidence

The Cochrane Collaboration tools(*32*) were used to assess the likelihood of bias in trials in the following areas: random sequence generation, assignment hiding, blind techniques, incomplete outcome data, and selective outcome reporting. The GRADE process (Grading of Recommendations, Assessment, Development and Evaluation) was used to evaluate the certainty of the evidence (*i.e.*, the certainty of the estimate) (*33*).

2.7. Statistical Analysis

R statistical software (version R 4.3.2) was used to conduct the statistical analysis for this study. The results were represented by logarithmically converting the predicted hazard ratios (HRs) with matching 95% confidence intervals (CIs) that were collected from the included trials. A random effect network meta-analysis under the frequentist framework was used to compare mixed treatments (*34*). League tables and forest graphs were produced by the network estimation process of the reverse transformation. Cochran's Q was used to evaluate heterogeneity between and within designs, and I^2 statistics were used to quantify heterogeneity. The I^2 values for low, moderate, and high levels of heterogeneity were less than 25%, 25% to 75%, and greater than 75%, respectively. The ranking of the processing was performed *via* P scores, which

are represented as frequency analogues under the cumulative ranking curve (SUCRA) (*35*). Rankgrams were plotted against P scores to visualize treatment rankings. A better therapeutic impact was indicated by a higher P score. NMA was performed with the "netmeta" R package.

3. Results

3.1. Study Selection

By using screening techniques for electronic searches, 409 titles and abstracts were ultimately identified, and 85 of these titles and abstracts could be evaluated (Figure 1). Seven total references were found (*9,19-23,36*).

3.2. Study Characteristics

Seven identified first-line trials involved a total of 4033 patients (*9,19-23,36*). A first-line systemic chemotherapy regimen for patients with advanced BTC for the subsequent ten years was established in 2010 by the ABC-02 trial (*9*), which compared the use of gemcitabine alone with gemcitabine + cisplatin (GemCis). The GemCis dual chemotherapy regimens were compared across six trials (S-1 + GemCis, durvalumab + GemCis, pembrolizumab + GemCis, S-1 + gemcitabine, nab-paclitaxel + GemCis, NUC-1031 + cisplatin) (*19-23,36*) (Supplementary Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*). The age range of the patients included in the trials was 20-85 years (Table 1).

3.3. Network Meta-analysis

A PFS benefit was observed in the network meta-analysis when comparing durvalumab + GemCis triple therapy versus GemCis double therapy (HR, 0.75; 95% CI, 0.63–0.89), S-1 + GemCis triple therapy versus GemCis double therapy (HR, 0.75; 95% CI, 0.58–0.97), and pembrolizumab + GemCis triple therapy versus GemCis double therapy (HR, 0.86; 95% CI, 0.75–0.99). PFS was worsened with NUC-1031 plus cisplatin combination therapy (NUC-1031 is a phosphoramidate modification of gemcitabine) compared to GemCis (HR, 1.45; 95% CI, 1.21–1.73). Compared with that of GemCis double therapy, the PFS benefit of nab-

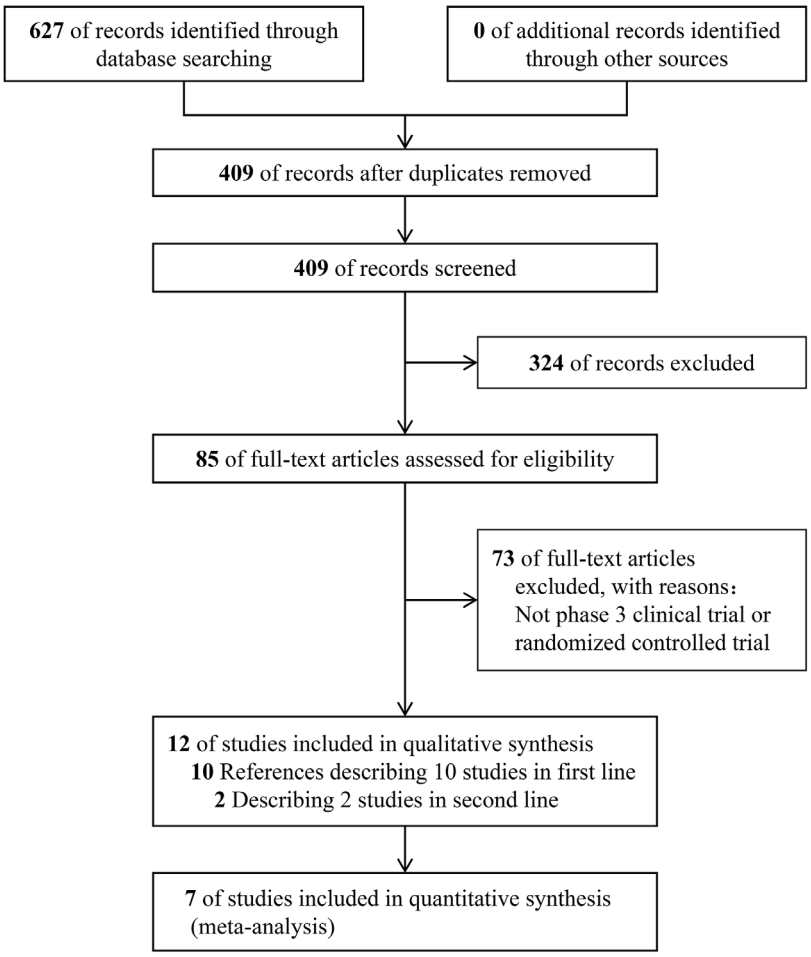

Figure 1. PRISMA flow diagram displaying the process of screening and choosing.

Table 1. Baseline characteristics for patients included in the first-line trials

Study Name	Arm	Patients	ECOG PS (0,1,2)%	Median Age (Range)	Race/Region	Sex (male %)
Valle J 2010 (ABC-02)	GemCis	204	0 (32.4%),1 (54.4%), 2 (13.2%)	63.9 (32.8-81.9)	Britain	47.10%
	Gemcitabine	206	0 (31.1%),1 (56.8%), 2 (11.7%),unknown (0.5%)	63.2 (23.4-84.8)		47.60%
Morizane C 2019 (JCOG1113)	Gemcitabine + S-1	179	0 (69.3%),1 (30.7%)	67 (27-79)	Japan	54.20%
	GemCis	175	0 (74.3%),1 (25.7%)	67 (41-78)		56.60%
Oh DY 2022 (TOPAZ-1)	GemCis + Durvalumab	341	0 (50.7%),1 (49.3%)	64 (20-84)	multinational	49.60%
	GemCis	344	0 (47.4%),1 (52.6%)	64 (31-85)		51.20%
Kelley RK 2023 (KEYNOTE-966)	GemCis + Pembrolizumab	533	0 (48%),1 (51%),2 (<1%)	64.0 (57.0-71.0)	multinational	53%
	GemCis	536	0 (43%),1 (57%)	63.0 (55.0-70.0)		51%
Rachna T 2023 (SWOG 1815)	GemCis + Nab-paclitaxel	441 (2:1)	NR	NR	NR	45%
	GemCis					
Ioka T 2023 (KHBO1401-MITS)	GemCis + S-1	246 (1:1)	0-1 (98.4%),2 (1.6%)	68 (40-84)	Japan	53.70%
	GemCis		0-1 (100%)	68 (39-81)		55.30%
Knox J 2023	NUC-1031 + Cisplatin	828 (1:1)	NR	65	NR	53.40%
	GemCis					

Abbreviation: GemCis, Gemcitabine + Cisplatin. NR, not reported. ECOG PS: ECOG performance-status score, ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning.

paclitaxel + GemCis triple therapy and gemcitabine + S-1 double therapy was not inferior (Figure 2 and Supplementary Table S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*).

In terms of improving OS, the combination of durvalumab + GemCis triple therapy (HR, 0.80; 95% CI, 0.66–0.98) and pembrolizumab + GemCis triple therapy (HR, 0.83; 95% CI, 0.72–0.95) was superior to GemCis combination therapy. Compared with those of GemCis, the OS benefits of nab-paclitaxel + GemCis, S-1 + gemcitabine, and GemCis + S-1 were noninferior (Figure 2 and Supplementary Table S2, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*).

The highest durvalumab + GemCis ranking for PFS (P score = 87.81%) and the highest S-1 + GemCis ranking for OS (P score = 81.43%) matched these results (Figure 3 and Supplementary Table S3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*).

3.4. Risk of Bias and Certainty of Evidence

Via the Cochrane method for assessing the risk of bias, a qualitative assessment was performed by evaluating several indicators for each unique study. With two trials blindly assessing the outcome evaluators and the remaining trials either not performing blind assessments or not clearly performing blind assessments, the trial was deemed to have overcome the overall low-risk bias (Figure 4). The certainty of indirect comparative evidence was deemed to be generally high (Supplementary Table S4 and S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=229*).

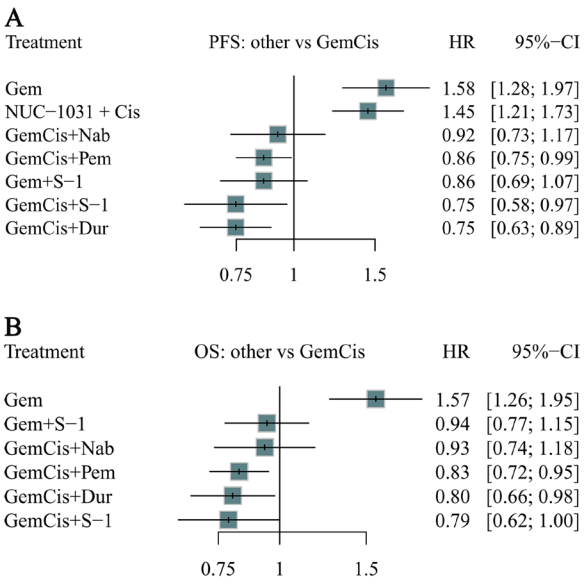

Figure 2. Forest plot of Frequentist network meta-analysis using random-effects model. (A) Progression-free survival (PFS). **(B)** Overall survival (OS). *Abbreviation*: Gem: gemcitabine; Cis: cisplatin; GemCis: gemcitabine + cisplatin; Nab: nab-paclitaxel; Pem: pembrolizumab; Dur: durvalumab.

4. Discussion

The prognosis for advanced BTC patients is currently poor, and patients can respond differently to various

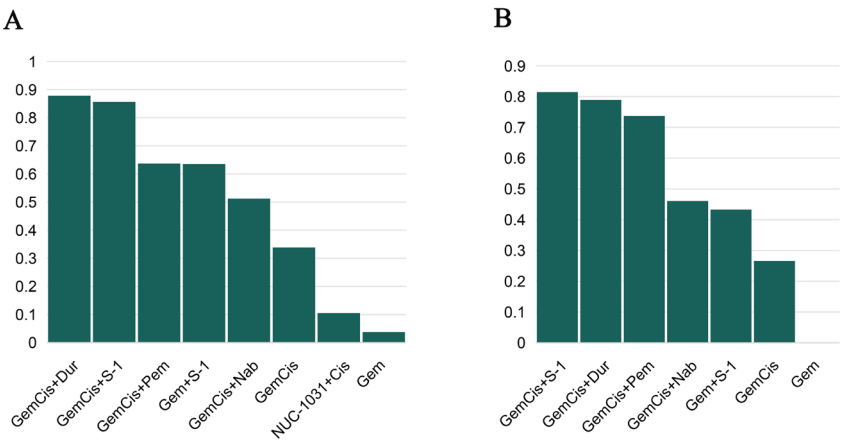

Figure 3. Ranking of 1st line treatments. (A) Progression-free survival (PFS). **(B)** Overall survival (OS). *Abbreviation*: Gem: gemcitabine; Cis: cisplatin; GemCis: gemcitabine + cisplatin; Nab: nab-paclitaxel; Pem: pembrolizumab; Dur: durvalumab.

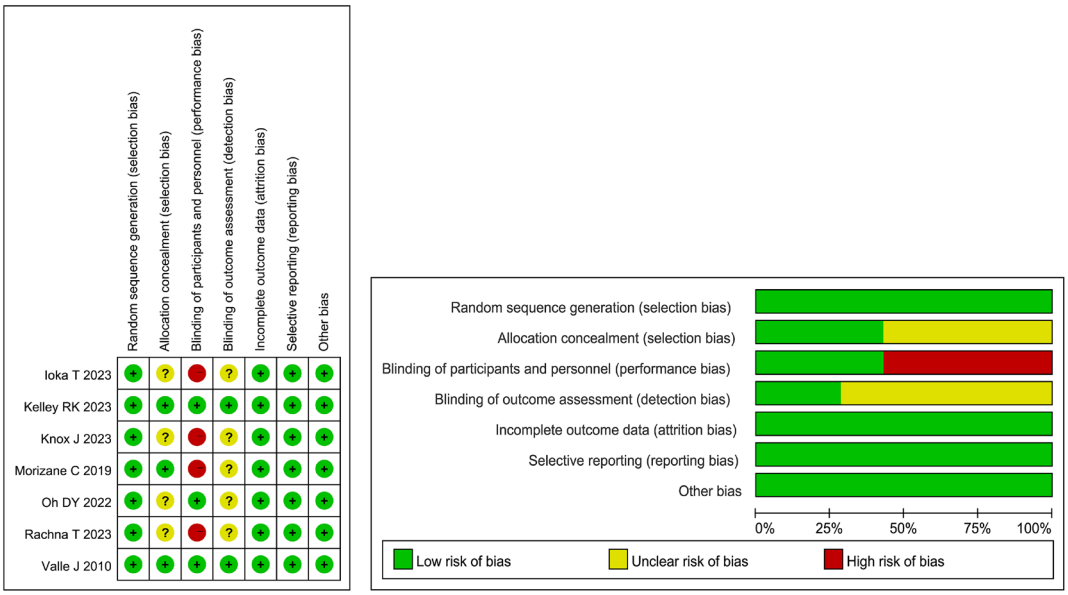

Figure 4. Risk of bias graph for first-line studies: review authors' judgements about each risk of bias item presented as percentages across all included studies.

treatment plans. For this reason, it is critical to compare the benefits of current regimens and increase their efficacy to develop a better treatment plan. Therefore, we ranked first-line systemic therapy regimens for advanced BTC *via* this systematic review and network meta-analysis and found that durvalumab + GemCis is likely to be the best available treatment combination. According to the P score, the durvalumab + GemCis triple therapy has more advantages in terms of evidence certainty and risk of bias, and the Chinese Society of Clinical Oncology guidelines also recommend it as a first-line treatment for advanced BTC level I patients and S-1 + GemCis triple therapy as a first-line treatment for advanced BTC level II patients. Therefore, we prefer durvalumab + GemCis triple therapy as the preferred option. Despite having a low P score, nab-paclitaxel + GemCis was ranked first (8.2 months) solely based on PFS length. The best prescription schedule can be chosen based on the particular circumstances (such as patient location and ethnicity, among other factors) and paired with the economy of care. Simultaneously, treatment approaches such as radiation embolization (*37*) or hepatic artery infusion chemotherapy (*38*) have been developed that combine systemic therapy with local treatments.

Chemotherapy may stimulate the patient's immune response (*39*), and its combination with ICIs may enhance the therapeutic effect. Gemcitabine has been shown to enhance the antitumour immune response (*40,41*). Moreover, the anticancer activity of cisplatin is not solely limited to its ability to inhibit mitosis; rather, it also has important immunomodulatory effects, such as upregulated major histocompatibility complex (MHC) class I expression and a downregulated

immunosuppressive microenvironment (*42*). This provides a reasonable explanation for the results that were obtained in this study.

For advanced BTC, ICIs such as durvalumab have become more crucial in treatment, even though chemotherapy treatment (such as *via* GemCis) is still the primary treatment choice. Moreover, tailored treatments are being quickly developed. Numerous studies have shown that advanced BTCs have a high rate of targetable somatic cell transformation (*43*). Mutations in IDH-1 and IDH-2 (*44*), as well as FGFR rearrangement or fusion (*13*), are two examples of types of transformation. Thus far, several medications have been approved by the Food and Drug Administration (FDA) to treat these BTC changes, including futibatinib (*45*) and pemigatinib (*46*), which target FGFR-2 fusions, and ivosidenib (*47*), which targets IDH-1 mutations; all of these medications are included in the European Association for the Study of the Liver (EASL) and International Liver Cancer Association (ILCA) Clinical Practice Guidelines for the management of intrahepatic cholangiocarcinoma (iCCA) as second-line treatments (*48*).

Due to the fact that most of the information in this study was derived from indirect comparisons, its limitations are related to the nature of the network analysis. Furthermore, the study included only research-quality data rather than specific patient data, which limits its applicability. The ranking probability of the comparative efficacy of various therapies was also estimated *via* the SUCRA curve; however, this method has limitations, and the findings should be evaluated with caution. Despite these drawbacks, this research may contribute to a better understanding of how first-line systemic treatment for advanced BTC is currently evolving.

In conclusion, durvalumab + GemCis is currently the most effective systemic therapy for advanced BTC. Future trials should focus on other possible combinations, as well as sequencing and targeted therapy.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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