REVIEW

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The Ideal Second-Line Treatment Options for Patients with Advanced Biliary Tract Cancer Refractory to Gemcitabine-Based First-Line Chemotherapy: A Result From Bayesian Network-Meta Analysis

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Abstract

Objective: To determine the most ideal second-line treatment for advanced biliary tract cancer, considering the response rate, survival, and drug adverse events. **Methods:** This network meta analysis (NMA) was conducted in accordance with the PRISMA with NMA extension guidance. After formulation of PICO, comprehensive searches of literatures were done including all randomized controlled studies that reported the second-line treatment for advanced biliary tract cancers' subjects who have failed with first-line gemcitabine-based chemotherapy. The outcomes analyzed were response rate, progression-free survival, overall survival, and serious adverse events. Data were collected and analysis will be done based on Bayesian method using BUGSnet package in R studio. **Results:** Eleven eligible RCTs were included in this NMA with 1228 subjects and 15 different second-line therapies. The NMA was conducted in random-effects, consistent, and convergence model. Most studies reported the use of fluoropyrimidine-based regimen, either alone or in combination with others drugs. The combination of 5FU-LV with liposomal irinotecan showed the most favorable outcomes, the highest response rate, longest overall survival, and longest progression-free survival. However, this regimen had highest adverse events among others. The next promising regimen was combination of oral capecitabine with varlitinib, with favorable response rate (RR 16.67; 95%CI 0.01 to 21.39), overall survival (HR 0.09; 95%CI -5.22 to 5.37), and progression-free survival (HR 1.37; 95%CI -58.4 to 62.15). The serious adverse events were reported less than others. **Conclusion:** The combination of oral capecitabine with varlitinib could be a promising second-line treatment for patients with advanced biliary tract cancer refractory to gemcitabine-based first-line regimen.

Keywords: Advanced biliary tract cancer- Second-line treatment- Response rate

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Introduction

Advanced biliary tract cancer (BTC) is a rare and highly aggressive malignancy that encompasses cancers of the bile ducts, gallbladder, and ampulla of Vater. It is associated with poor prognosis and has limited therapeutic options. The majority of BTC patients are diagnosed at an advanced or unresectable stage, which significantly limits the potential for surgical intervention. As a result, systemic chemotherapy remains the cornerstone of treatment for advanced BTC. The standard first-line chemotherapy regimen consists of gemcitabine-based therapy, often combined with cisplatin or other agents [1]. While gemcitabine-based chemotherapy has been the standard of care, its clinical efficacy remains suboptimal, with reported response rates typically under 30%. This highlights a critical gap in the treatment of BTC, where progression of disease after first-line therapy leaves patients with limited survival prospects and necessitates effective second-line therapeutic strategies [2].

Despite the substantial clinical need for an optimal second-line treatment strategy, no standardized guidelines currently exist. The heterogeneity of patient populations, tumor biology, and treatment response has led to the exploration of numerous second-line therapy options, but the clinical evidence is far from definitive. Among the most frequently investigated treatments are fluoropyrimidine-based combinations, such as 5-fluorouracil (5-FU) or capecitabine, and novel targeted agents, which include inhibitors of key molecular pathways involved in tumor growth and resistance [3]. However, the variability in efficacy, toxicity profiles, and treatment outcomes complicates treatment decision-making, especially in the context of patients who have progressed on gemcitabine-based therapies.

Given the absence of definitive guidance and the

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diverse range of second-line options, this study seeks to provide a comprehensive evaluation of the available treatments for advanced BTC patients who are refractory to gemcitabine-based therapy. Network meta-analysis (NMA), a statistical approach that allows for the comparison of multiple treatment options in a single analysis, offers a powerful tool to address this gap in the literature. By synthesizing data from randomized controlled trials (RCTs) across various regimens, a Bayesian network meta-analysis can generate a more robust comparison of second-line therapies, accounting for both direct and indirect treatment effects. This approach is particularly valuable in the context of rare cancers, where individual studies may be underpowered, and where evidence from multiple sources must be integrated to draw meaningful conclusions [4].

The primary objective of this study is to identify the most effective and tolerable second-line treatment strategies for patients with advanced BTC who have not responded to gemcitabine-based chemotherapy. By evaluating the relative efficacy and safety profiles of these therapies, we aim to inform clinical decision-making and guide future therapeutic development in the management of advanced BTC. Furthermore, this network meta-analysis will provide insights into the comparative effectiveness of targeted therapies versus conventional chemotherapy regimens, thus contributing to a deeper understanding of treatment paradigms in this challenging disease.

Materials and Methods

Study Design

This study is a Bayesian network meta-analysis (NMA) conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) with NMA extension guidelines. The analysis integrates data from randomized controlled trials (RCTs) to compare the efficacy and safety of second-line treatments for advanced biliary tract cancer (BTC) patients who are refractory to gemcitabine-based first-line chemotherapy.

PICO Formulation

Population

Patients with advanced biliary tract cancer who have failed first-line gemcitabine-based chemotherapy (stable or progressive disease based on RECIST criteria). Intervention: Second-line treatment regimens, including fluoropyrimidine-based regimens and novel targeted therapies. Comparator: Other second-line treatments or placebo (if applicable). Outcomes: Primary outcomes include response rate (RR), progression-free survival (PFS), overall survival (OS), and serious adverse events (SAEs).

Data Collection

A comprehensive literature search was conducted across databases including PubMed, Embase, Cochrane Library, and clinical trial registries. The search included RCTs evaluating second-line treatment options for advanced BTC published up to the present. Studies were included if they involved patients with advanced BTC refractory to gemcitabine-based chemotherapy and compared two or more treatment regimens. Data extracted included study characteristics, patient demographics, treatment regimens, and outcome measures. Two reviewers independently screened titles, abstracts, and full texts, with disagreements resolved by consensus.

Data Analysis

Bayesian NMA was performed to synthesize evidence and compare treatments across multiple trials. Consistency and transitivity assumptions were assessed to ensure valid comparisons. The NMA framework employed a random-effects model to account for between-study variability. Results were presented as: Response rates, PFS and OS (hazard ratios with 95% credible intervals)., and SAEs. Outcomes were ranked using surface under the cumulative ranking curve (SUCRA) values to identify the most effective and safe treatment regimens.

Statistical Analysis

Bayesian analysis was conducted using the BUGSnet package in R Studio. A Markov Chain Monte Carlo (MCMC) algorithm was used to generate posterior distributions for the treatment effects. Convergence Assessment used Gelman-Rubin diagnostics and trace plots were used to evaluate model convergence. Model Fit used Deviance information criterion (DIC) was calculated to compare model fits. Results were visualized using league tables, forest plots, and SUCRA plots to rank treatment regimens. All statistical analyses were conducted in R Studio, and the code was reviewed to ensure reproducibility and robustness of findings.

Results

Study Selection and Characteristics

The search yielded 11 eligible RCTs [5-10, 3, 11-14] involving 1,228 patients with advanced biliary tract cancer refractory to gemcitabine-based first-line chemotherapy (Figure 1). These trials evaluated 15 different second-line regimens, with most studies focusing on fluoropyrimidine-based combinations. Key study characteristics, including population demographics, treatment regimens, and outcomes assessed, are summarized in Table 1.

Network Meta-Analysis

The network plot (Figure 2) illustrates the treatment comparisons across the included studies. Fluoropyrimidine-based regimens, either as monotherapy or in combination with other agents, formed the core of the treatment network, with 5FU-LV plus liposomal irinotecan and capecitabine plus varlitinib being the most studied combinations.

Outcomes

Response Rate (RR)

The combination of 5FU-LV and liposomal irinotecan demonstrated the highest response rate among all regimens, significantly outperforming most comparators.

Table 1. Study Characteristics

Author	Study type	Second-line chemotherapy regimen	N	Response rate	Overall survival	Adverse effect
Javle [5]	RCT phase II	Capecitabine + varlitinib	64	6	7.8 (1.1)	25
		Capecitabine	63	3	7.5 (0.7)	27
Yoo [13]	RCT phase II	FOLFIRI (liposomal)	88			37
		5FU-LV	86			21
Zheng [14]	RCT phase II	IRI	30	2	7.3 (1.2)	23
		XELIRI	30	4	10 (1.7)	27
Brieau [7]	RCT phase II	FOLFIRI	61	7	6.7 (1.1)	
		5FU-LV + cisplatin	37	5	6.1 (1.9)	
		5FU-LV + capecitabine	37	4	7.1 (1.7)	
		FOLFOX	20	2	6.1 (0.9)	
		Sunitib	9	1	8.4 (3.5)	
Choi [8]	RCT phase II	FOLFOX	51	3	6.3 (1.9)	31
		FOLFIRI	50	2	5.7 (1.0)	29
Demols [9]	RCT phase II	Regorafenib	33	8	5.3 (2.6)	12
		Placebo	33	3	5.1 (2.1)	8
Ueno [6]	RCT phase II	Resminostat	50	3	7.8 (1.6)	27
		Placebo	51	5	7.5 (1.5)	15
Kim [10]	RCT phase II	Trametinib	24	2	4.3 (1.9)	7
		5FU-LV + capecitabine	20	2	6.6 (2.8)	8
Cereda [11]	RCT phase II	Capecitabine	26	0	9.5 (6.5)	8
		Capecitabine + mitomycin	29	1	8.1 (7.0)	9
Lamarca [3]	RCT phase III	FOLFOX	81	0	6.2 (0.8)	42
		Placebo	81	4	5.3 (0.6)	56
Hyung [12]	RCT phase II	FOLFIRI (liposomal)	86	17	8.6 (4.8)	
		5FU-LV	86	2	5.3 (1.9)	

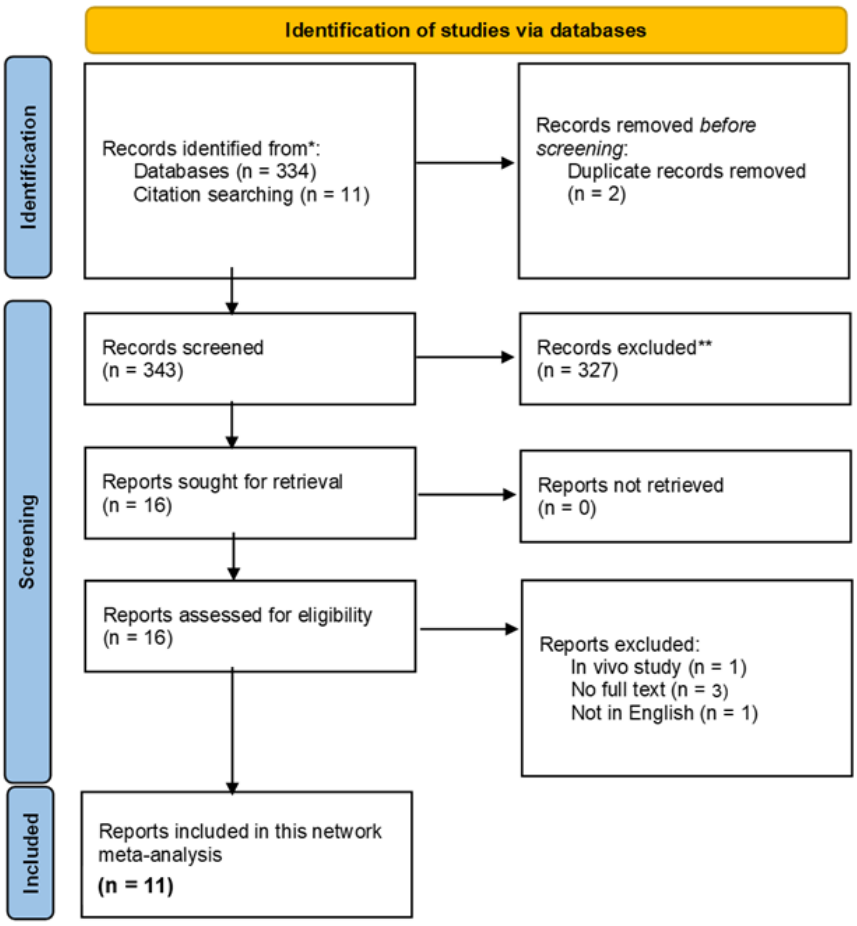

Figure 1. PRISMA Flowchart of This Study

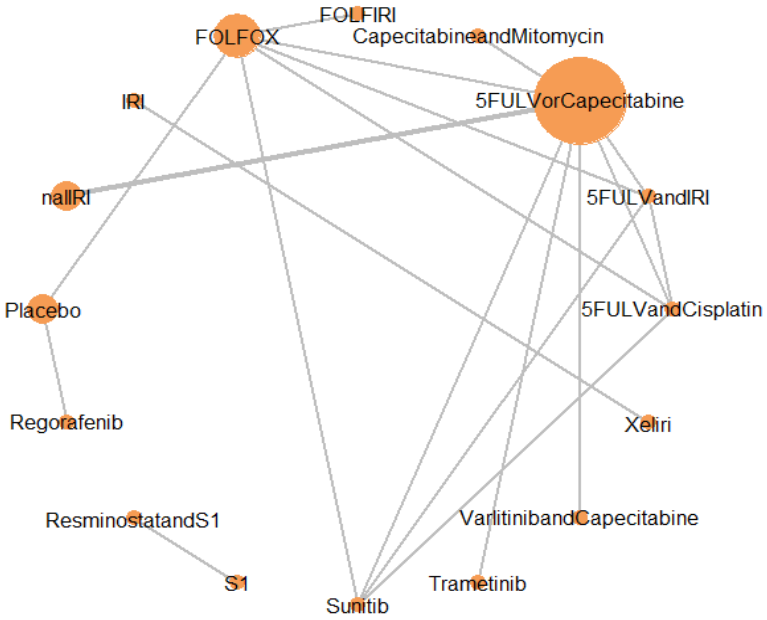

Figure 2. Network Plot of Trials

Capecitabine plus varlitinib also showed promising RR but was slightly less effective (Figure 3).

Overall Survival (OS)

The combination of 5FU-LV and liposomal irinotecan was associated with the longest OS. Capecitabine plus varlitinib showed a comparable OS benefit with fewer adverse events (Figure 4).

Progression-Free Survival (PFS)

5FU-LV plus liposomal irinotecan achieved the longest median PFS, closely followed by capecitabine plus varlitinib. Both regimens were significantly superior to other treatments in terms of delaying disease progression (Figure 5).

Safety Outcomes

The combination of 5FU-LV and liposomal irinotecan had the highest rate of serious adverse events (SAEs) compared to other treatments, limiting its tolerability. Capecitabine plus varlitinib exhibited a favorable safety profile with a lower incidence of SAEs, making it an attractive alternative for second-line therapy (Figure 6).

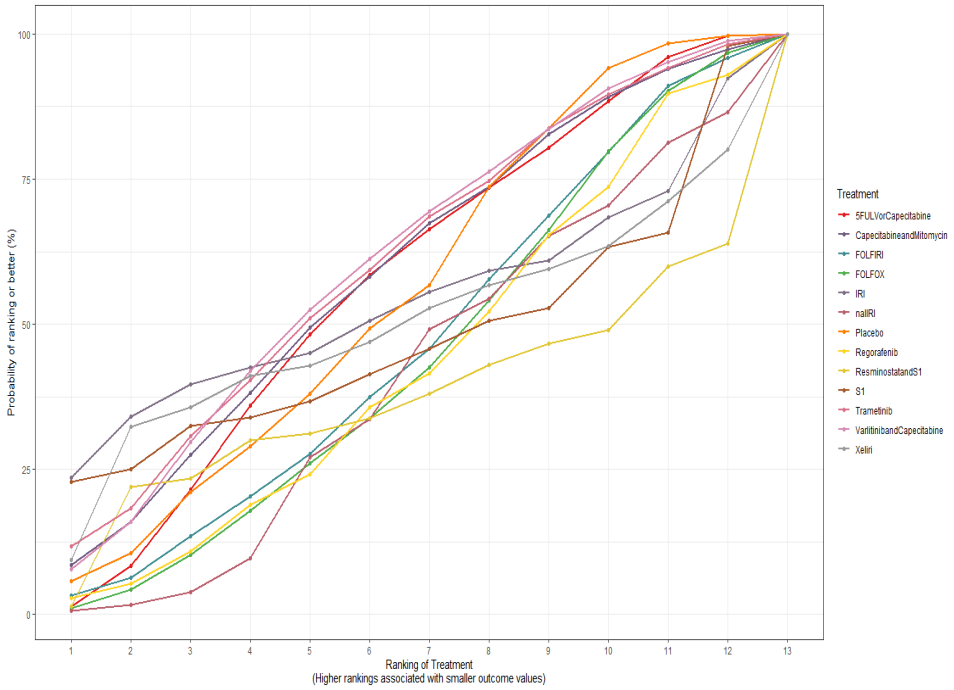

Figure 3. SUCRA Plot Showed the Ranking of Response Rates among Second-Line Treatment in Advanced Biliary Tract Cancers

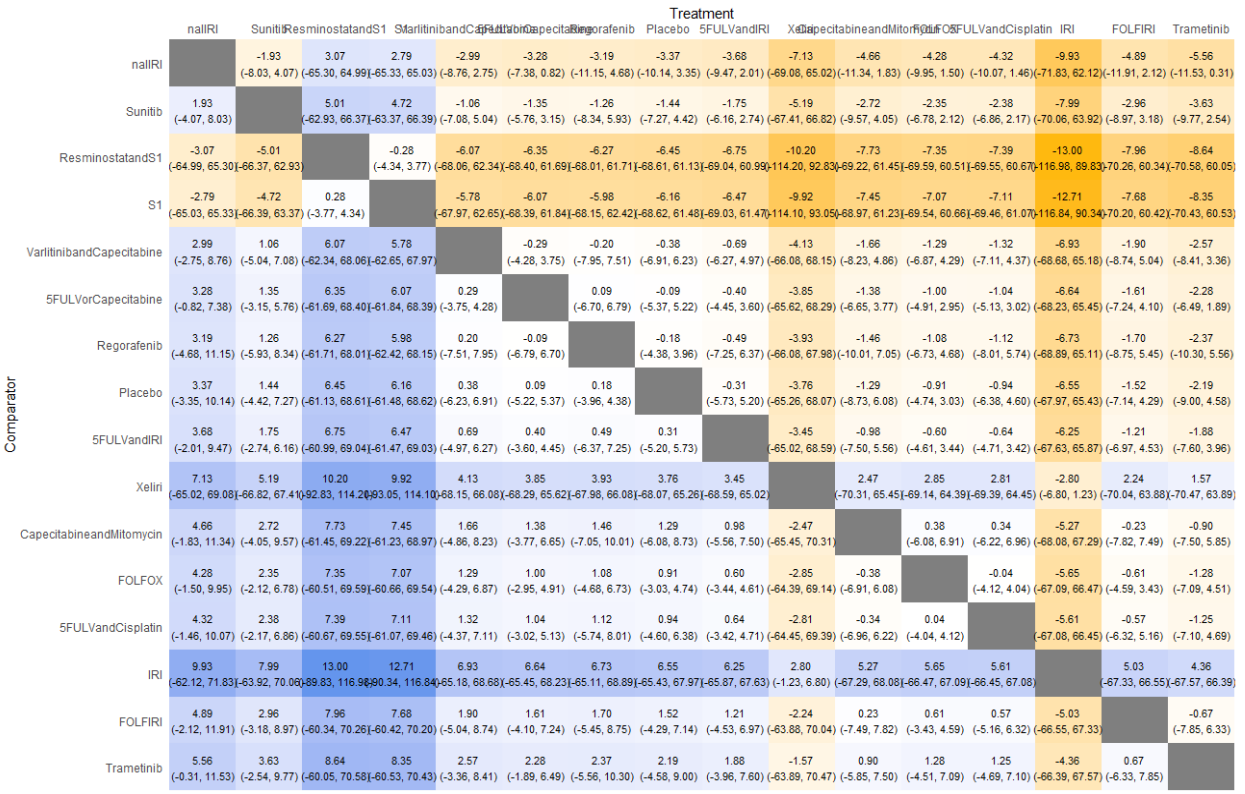

Figure 4. Forest Plot Showed the Overall Survival among Second-Line Treatment in Advanced Biliary Tract Cancers

Discussion

This network meta-analysis provides critical insights into the optimal second-line treatment options for patients with advanced biliary tract cancer (BTC) refractory to gemcitabine-based first-line chemotherapy. Among 15 regimens evaluated across 11 RCTs, the combination of 5FU-LV and liposomal irinotecan emerged as the most

Figure 5. Forest Plot Showed the Progression-Free Survival among Second-Line Treatment in Advanced Biliary Tract Cancers

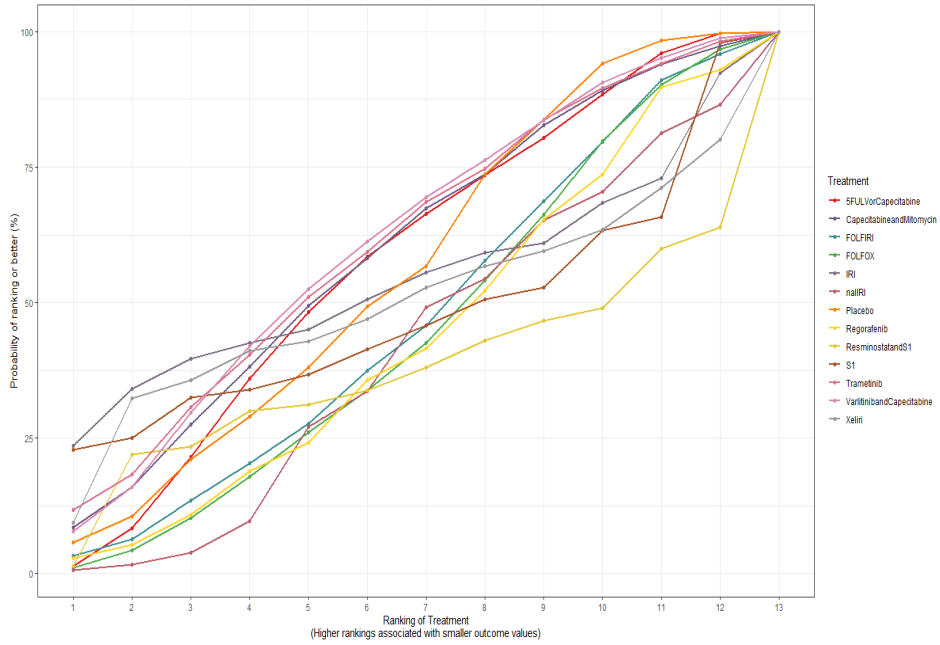

Figure 6. SUCRA Plot Showed the Ranking of Adverse Effects among Second-Line Treatment in Advanced Biliary Tract Cancers

effective in terms of response rate, progression-free survival (PFS), and overall survival (OS). However, its high rate of serious adverse events (SAEs) poses challenges for clinical use. Capecitabine plus varlitinib offers a promising alternative with a more favorable balance between efficacy and safety.

The superior efficacy of 5FU-LV plus liposomal irinotecan is consistent with prior studies highlighting the benefits of irinotecan-based regimens in refractory gastrointestinal malignancies [3]. This combination exploits the synergistic effects of fluoropyrimidines and irinotecan, effectively targeting resistant cancer cells.However, its high toxicity profile, including gastrointestinal and hematologic adverse events, necessitates careful patient selection and supportive care.

Capecitabine plus varlitinib, a regimen integrating oral fluoropyrimidines with a targeted agent, demonstrated comparable efficacy with fewer SAEs. Varlitinib's dual inhibition of HER2 and EGFR signaling pathways may account for its ability to suppress tumor progression while minimizing systemic toxicity [5]. This aligns with emerging evidence suggesting the potential of targeted therapies in BTC, particularly in combination with standard chemotherapy.

The lack of standardized second-line treatment guidelines for advanced BTC complicates decision-making for clinicians. The findings of this study support a tailored approach, with 5FU-LV plus liposomal irinotecan as the preferred option for patients with good performance status and tolerance for intensive treatment. In contrast, capecitabine plus varlitinib offers a viable alternative for frailer patients or those at high risk of treatment-related toxicities. Additionally, the inclusion of multiple fluoropyrimidine-based regimens in the network underscores the importance of this class of drugs as a cornerstone of BTC management. The promising results for targeted therapies, such as varlitinib, further highlight the potential of precision oncology in improving outcomes for this challenging malignancy [15].

This study is the first to use a Bayesian framework for NMA in advanced BTC, allowing robust comparisons across multiple treatments. The use of a consistent random-effects model and comprehensive assessment of transitivity and model fit enhances the reliability of the findings. However, the analysis is limited by the heterogeneity of included studies, particularly in terms of patient populations and outcome reporting. Furthermore, the small sample sizes in some trials and the lack of direct head-to-head comparisons for certain regimens may introduce bias.

Future research should focus on conducting large-scale, well-designed RCTs to validate the findings of this study. The role of targeted agents, immunotherapies, and combination strategies warrants further investigation, particularly in biomarker-selected population [8]. Real-world studies are also essential to assess the generalizability and cost-effectiveness of these regimens.

In conclusion, the combination of oral capecitabine with varlitinib could be a promising second-line treatment for patients with advanced biliary tract cancer refractory to gemcitabine-based first-line regimen.

Author Contribution Statement

ES: concepts, design, statistical analysis, discussion, manuscript preparation and editing. CA: concept, data collection, data analysis, discussion, and conclusion.

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Availability of data

Data were available on request to corresponding author.

Conflict of interest

The authors declared that there was no conflict of interest in this study.

References

1. Rizzo A, Brandi G. Adjuvant systemic treatment in resected biliary tract cancer: State of the art, controversies, and future directions. Cancer Treat Res Commun. 2021;27:100334. https://doi.org/10.1016/j.ctarc.2021.100334.
2. Goetze TO, Bechstein WO, Bankstahl US, Keck T, Königsrainer A, Lang SA, et al. Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone with or without adjuvant chemotherapy in incidentally detected gallbladder carcinoma after simple cholecystectomy or in front of radical resection of btc (icc/ecc) - a phase iii study of the german registry of incidental gallbladder carcinoma platform (gr)- the aio/ calgp/ aco- gain-trial. BMC cancer. 2020;20(1):122. https://doi.org/10.1186/s12885-020-6610-4.
3. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line folfox chemotherapy versus active symptom control for advanced biliary tract cancer (abc-06): A phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021;22(5):690-701. https://doi.org/10.1016/s1470-2045(21)00027-9.
4. Rouse B, Chaimani A, Li T. Network meta-analysis: An introduction for clinicians. Intern Emerg Med. 2017;12(1):103-11. https://doi.org/10.1007/s11739-016-1583-7.
5. Javle MM, Oh DY, Ikeda M, Yong WP, Hsu K, Lindmark B, et al. Varlitinib plus capecitabine in second-line advanced biliary tract cancer: A randomized, phase ii study (treetopp). ESMO open. 2022;7(1):100314. https://doi.org/10.1016/j.esmoop.2021.100314.
6. Ueno M, Morizane C, Furukawa M, Sakai D, Komatsu Y, Nakai Y, et al. A randomized, double-blind, phase ii study of oral histone deacetylase inhibitor resminostat plus s-1 versus placebo plus s-1 in biliary tract cancers previously treated with gemcitabine plus platinum-based chemotherapy. Cancer Med. 2021;10(6):2088-99. https://doi.org/10.1002/cam4.3813.
7. Brieau B, Dahan L, De Rycke Y, Boussaha T, Vasseur P, Tougeron D, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: A large multicenter study by the association des gastro-entérologues oncologues. Cancer. 2015;121(18):3290-7. https://doi.org/10.1002/cncr.29471.
8. Choi IS, Kim KH, Lee JH, Suh KJ, Kim JW, Park JH, et al. A randomised phase ii study of oxaliplatin/5-fu (mfolfox) versus irinotecan/5-fu (mfolfiri) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur j cancer. 2021;154:288-95. https://doi.org/10.1016/j.ejca.2021.06.019.
9. Demols A, Borbath I, Van den Eynde M, Houbiers G, Peeters M, Marechal R, et al. Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced/metastatic biliary tumors: Reachin, a randomized, double-blind, phase ii trial. Ann oncol. 2020;31(9):1169-77. https://doi.org/10.1016/j.annonc.2020.05.018.
10. Kim RD, McDonough S, El-Khoueiry AB, Bekaii-Saab TS, Stein SM, Sahai V, et al. Randomised phase ii trial (swog s1310) of single agent mek inhibitor trametinib versus 5-fluorouracil or capecitabine in refractory advanced biliary cancer. Eur j cancer. 2020;130:219-27. https://doi.org/10.1016/j.ejca.2020.01.026.
11. Cereda S, Milella M, Cordio S, Leone F, Aprile G, Galiano A, et al. Capecitabine with/without mitomycin c: Results of a randomized phase ii trial of second-line therapy in advanced biliary tract adenocarcinoma. Cancer Chemother Pharmacol. 2016;77(1):109-14. https://doi.org/10.1007/s00280-015-2919-0.
12. Hyung J, Kim I, Kim KP, Ryoo BY, Jeong JH, Kang MJ, et al. Treatment with liposomal irinotecan plus fluorouracil and leucovorin for patients with previously treated metastatic biliary tract cancer: The phase 2b nifty randomized clinical trial. JAMA oncol. 2023;9(5):692-9. https://doi.org/10.1001/jamaoncol.2023.0016.
13. Yoo C, Kim KP, Jeong JH, Kim I, Kang MJ, Cheon J, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (nifty): A multicentre, open-label, randomised, phase 2b study. Lancet Oncol. 2021;22(11):1560-72. https://doi.org/10.1016/s1470-2045(21)00486-1.
14. Zheng Y, Tu X, Zhao P, Jiang W, Liu L, Tong Z, et al. A randomised phase ii study of second-line xeliri regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin. Br j cancer. 2018;119(3):291-5. https://doi.org/10.1038/s41416-018-0138-2.
15. Hwang I, Han S, Jeong JH, Ihm C, Rhee TG, Shim SR. The efficacy of second-line chemotherapy for advanced biliary tract cancer: A systematic review and network meta-analysis. J Hepatobiliary Pancreat Sci. 2025;32(4):265-75. https://doi.org/10.1002/jhbp.12113.