Highlights in 2023 ESMO congress biliary tract cancer session

Nan Zhang,[1,2] Mingjian Piao,[1,2] and Haitao Zhao[1,*]

[1]Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

[2]These authors contributed equally

*Correspondence: zhaoht@pumch.cn

Received: November 19, 2023; Accepted: December 22, 2023; Published Online: January 11, 2024; https://doi.org/10.59717/j.xinn-med.2024.100047

Citation: Zhang N., Piao M., and Zhao H. (2024). Highlights in 2023 ESMO congress biliary tract cancer session. The Innovation Medicine **2(1)**: 100047.

Figure 1. The five highlights were presented at the ESMO congress BTC session These highlights include: (1) the first application of immunotherapy in neoadjuvant treatment for localized BTC and analysis of large phase III clinical trials in aBTC, (2) real-world studies on the treatment of BTC, (3) further exploration of precision medicine, (4) non-invasive genetic testing and prognosis prediction using liquid biopsy, (5) the use of AI in biomarker exploration and pathological slide review. Abbreviations: ESMO, European Society for Medical Oncology; BTC, biliary tract cancer; aBTC, advanced biliary tract cancer; AI, artificial intelligence.

The 2023 European Society for Medical Oncology (ESMO) annual conference, held in Madrid, Spain, from October 20th to 24th, covered exciting topics in biliary tract cancer (BTC) treatment, including exploring new regimens, studying biomarkers, applying artificial intelligence (AI) in research, and analyzing real-world clinical treatment status (Figure 1).

CLINICAL TRIALS ARE SPLENDID AND DIVERSE

Clinical trials, exemplified by the prospective randomized trial DEBATE (NCT04308174) focusing on the perioperative period, have revolutionized neoadjuvant therapy for BTC. In this study of 45 patients, combining durvalumab with gemcitabine and cisplatin (D + GC) demonstrated superior response rates (36% vs. 7%) and curative-intent resection rates (61% vs. 36%) compared to GC chemotherapy alone. Prior to this, immunotherapy had only been demonstrated to improve the survival of patients with advanced biliary tract cancer (aBTC) in the phase III TOPAZ-1 study (D + GC).[1] Moreover, this study was the first to demonstrate immunotherapy efficacy in localized BTC. The DEBATE study revealed that, as a neoadjuvant approach, GC chemotherapy combined with immunotherapy demonstrated significantly improved efficacy in localized BTC compared to traditional chemotherapy, rendering it a practical neoadjuvant strategy. Specifically, a five-fold increase in response rates was demonstrated, indicating significant differences. The regimen induced a dramatic increase in the short-term overall tumor shrinkage rate, coupled with a significant improvement in long-term patient survival. Regarding the clinical characteristics, immunotherapy combined with chemotherapy in the neoadjuvant stage is particularly effective, possibly owing to the enhanced physical condition and more robust immune function of patients eligible for surgery. Previous studies have underscored the prognostic variability of BTC based on anatomical site, with gallbladder cancer (GBC) exhibiting the poorest prognosis;[2] however, subgroup analysis of corresponding patients has not yet been conducted.

Further analysis of several significant phase III first-line clinical trials has garnered attention. Post hoc analyses of ABC-01, ABC-02, and ABC-03 have augmented the understanding of clinical outcomes of GC chemotherapy regimens in patients with advanced BTC. These analyses revealed that extrahepatic cholangiocarcinoma (eCCA) prognosis across different anatomical sites is similar but worse than that of intrahepatic cholangiocarcinoma (iCCA). Regarding the TOPAZ-1 extension cohort in China, where 130 patients were subjected to a 1:1 randomization into the D+GC or GC arm, the clinical outcomes mirror those of the global cohort, addressing the data deficit for the Chinese aBTC population in the context of immunotherapy. Consequently, durvalumab has received approval for aBTC treatment in China. The KEYNOTE-966 study focused on patients with aBTC co-infected with hepatitis B virus and explored the safety of pembrolizumab plus GC chemotherapy in this population, yielding favorable outcomes.

REAL-WORLD STUDIES CONTRIBUTE NOVEL EVIDENCE FOR BTC TREATMENT

In a retrospective chart review survey (GARNET-2) encompassing 792 patients with aBTC from five European countries, real-world treatment patterns and efficacy were investigated. Less than half of the patients in this study received the standard first-line chemotherapy, whereas the remaining may have undergone alternative treatments. Only one-third of the patients received second-line treatment, and fewer received third-line treatment. The overall survival (OS) was 13 months, underscoring the limited access to

comparably efficacious treatments for patients with late-stage BTC, including those with cholangiocarcinoma, gallbladder cancer, and ampullary carcinoma, which significantly affecting their survival. Therefore, standardized treatment is required for these patients. Standardizing and widely adopting second-line or third-line therapy or immunotherapy is essential, as it can ensure broader benefits across the patient spectrum. Another real-world study involving 1,285 patients from the Spanish RETUD Registry showed that late-stage patients who received standard first-line chemotherapy (GC regimen) exhibited a median progression-free survival (PFS) of 5.5 months and a median OS of 11.6 months, providing a new reference for standardized chemotherapy in real-world settings.

PRECISION TREATMENT OF BTC REMAINS A FOCAL POINT OF DISCUSSION

At the ESMO conference, several studies describing the genomic profile of BTC were discussed. An analysis of the population of the BILCAP study, where capecitabine was investigated as a postoperative adjuvant treatment regimen, showed that patients with EGFR amplification exhibit significantly reduced OS and PFS. Regarding young-onset BTC, a study found that actionable molecular alterations exhibited minimal variance compared to those in non-early onset patients and that CDKN2A mutation frequency was lower, suggesting that the biological mechanism driving young-onset BTC may differ from that in older patients, necessitating further investigation. Additionally, a study on genetic ancestries highlighted disparities between European and African BTC patients, revealing a younger median age at diagnosis, higher prevalence of female patients, higher ERBB2 alterations, TP53 prevalence, lower IDH1 expression, and prevalence of BRAF alterations among African BTC patients. Particularly notable is the higher prevalence of FGFR alterations among African patients with iCCA. Another study conducted in India demonstrated differences in BTC gene variations between northern and southern India, revealing substantial distinctions in the genomic landscape of Indian BTC compared to other global cohorts. However, neither study intricately delineated the alteration prevalence in specific BTC subtypes (iCCA, eCCA, and GBC). These studies suggest that racial differences play an essential role in BTC occurrence and development, prompting further research to predict different prognoses among different racial populations.

THE PROMINENCE OF LIQUID BIOPSY PERSISTS IN THE FIELD OF BTC RESEARCH

The analysis of tissue samples is constrained by limited puncture samples; however, circulating tumor DNA (ctDNA) detection can help address this limitation. Woo et al. investigated the concordance between ctDNA and tissue gene testing in a cohort of 102 patients with BTC (49.0% iCCA, 26.5% eCCA, and 24.5% GBC). The results revealed that the concordance between ctDNA and tumor tissue mutations demonstrated a sensitivity of 84.8% and a positive predictive value of 79.4%, indicating acceptable characteristics. Liquid biopsy can partially overcome the limitations of tissue gene testing. For many patients with BTC, obtaining tissue for biopsy is constrained, and the requirements for tissue testing may not be met, rendering liquid biopsy a solution to this drawback. Additionally, ctDNA facilitates dynamic monitoring of patient responses during drug treatment, enabling the exploration of drug resistance mechanisms. However, certain limitations persist, such as the correlation between the ability to detect gene mutations in plasma cfDNA and tumor burden, subject to influences from various factors affecting its release. This results in lower ctDNA concentrations in certain patients, prompting the imperative to address challenges associated with improving sequencing depth and sensitivity. Furthermore, the non-uniform shedding of ctDNA across primary tumors and metastases introduces uncertainty regarding the accurate representation of tumor heterogeneity by the detected alterations.[3] In addition, ctDNA is also used to detect postoperative minimal residual lesions. A study with a median follow-up duration of 20.5 months, focusing on the dynamic monitoring of tumor-informed ctDNA in 12 patients post-BTC surgery, showed that longitudinal negativity in ctDNA is correlated with improved recurrence-free survival.

ARTIFICIAL INTELLIGENCE PROVES INSTRUMENTAL IN ADVANCING BTC RESEARCH

Using AI-driven digital image analysis tools, a study analyzed 337 BTC hematoxylin and eosin (H&E)-stained whole-slide images (WSI). The results revealed that the immune phenotypes (IP) of patients could be divided into three categories based on the levels of tumor-infiltrating lymphocytes (TILs) and stromal TILs: inflammatory type (high TILs), immune exclusion type (low TILs and high matrix TILs), and immune desert type (low TILs). All the patients were administered PD-1 inhibitors, with 55.8% undergoing second-line therapy. Individuals with inflammatory IP exhibited better survival, response, and immune activation than those with non-inflammatory IP. Another study used an AI model to evaluate HER2 expression and TIL density in patients with advanced BTC. After screening the WSI of pretreatment HER2 immunohistochemistry slides and corresponding H&E-stained slides for 328 patients, the overall consistency between AI-derived scoring and pathologist-assessed HER2 categories was 75.3%. HER2-expressing tumors exhibited a significantly higher matrix TIL density than HER2-negative tumors. Furthermore, no significant difference in TIL density between tumors characterized by high and low HER2 expression was observed, consistent with the evaluation by AI and pathologists. Overall, AI-driven HER2 scoring was consistent with pathologist scoring, elucidating that HER2-expressing BTC tumors exhibit high matrix TILs.

CONCLUSION AND PERSPECTIVE

With the positive results observed in the TOPAZ-1 and KEYNOTE-966 phase III clinical trials, BTC treatment has entered the era of immunotherapy. Immunotherapy and precision therapy stand as imperative trajectories for the future BTC treatment paradigm. The continuous improvement of liquid biopsy technology and AI-driven big data can potentially facilitate enhanced identification of benefiting populations,[4] contributing substantially to the elimination of BTC. However, caution is warranted when using AI-driven models.[5] Defining the target population for the model, establishing evaluation models for epidemiology-based AI models, and accurately assessing the performance of the model, including repeatability, accuracy, and risk stratification, necessitate standardization and exploration in future endeavors. Additionally, the research goal remains clinical translation. Establishing a statistical model for estimating disease risk based on AI results will help clinical professionals render informed decisions. Thus, the development of corresponding guidelines emerges as a further imperative for AI-driven analysis.

REFERENCES

1. Oh, D.-Y., Ruth He, A., Qin, S., et al. (2022). Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid. **1**: EVIDoa2200015. DOI:10.1056/EVIDoa2200015.
2. Lamarca, A., Ross, P., Wasan, H.S., et al. (2020). Advanced Intrahepatic Cholangiocarcinoma: Post Hoc Analysis of the ABC-01, -02, and -03 Clinical Trials. J. Natl. Cancer Inst. **112**: 200–210. DOI:10.1093/jnci/djz071.
3. Nikanjam, M., Kato, S., and Kurzrock, R. (2022). Liquid biopsy: current technology and clinical applications. J. Hematol. Oncol. **15**: 1–14. DOI:10.1186/s13045-022-01351-y.
4. Xu, Y., Liu, X., Cao, X., et al. (2021). Artificial intelligence: A powerful paradigm for scientific research. The Innovation **2**: 100179. DOI:10.1016/j.xinn.2021.100179.
5. Egemen, D., Perkins, R.B., Cheung, L.C., et al. (2024). Artificial intelligence-based image analysis in clinical testing: Lessons from cervical cancer screening. J. Natl. Cancer Inst. **116**: 26-33. DOI: 10.1093/jnci/djad202.

FUNDING AND ACKNOWLEDGMENTS

This work was supported by the National High Level Hospital Clinical Research Funding [2022-PUMCH-B-128], CAMS Innovation Fund for Medical Sciences (CIFMS)[2022-I2M-C&T-A-003], CAMS Innovation Fund for Medical Sciences (CIFMS) [2021-I2M-1-061] [2021-I2M-1-003], and the National Ten-thousand Talent Program. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.