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First-line Treatment Selection for Advanced Unresectable Biliary Tract Cancer

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Introduction

Biliary tract cancer (BTC) comprises a group of heterogenous malignancies that arise from the bile ducts (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma) and the gallbladder (gallbladder cancer). Collectively, these malignancies carry a poor prognosis, which is attributed to the advanced stage at presentation. Historically, advanced BTC had a reputation of being less responsive to chemotherapy, a theory that was changed in the last decade, likely due to improved biliary drainage techniques that consequently improve liver function. Few advances have been made in the treatment of advanced and unresectable BTC in the past couple of years.

Overview of First-line Treatment

Chemotherapy

Before 2010, no standard chemotherapy regimen was available for treating advanced BTC. Patents were usually treated with chemotherapy used for pancreatic adenocarcinoma, such as gemcitabine or fluoropyrimidine as single agents or in combination with other drugs. Different chemotherapy combination regimens were primarily investigated in Phase II trials.

The Advanced Biliary Cancer (ABC-02) randomized phase III trial proved superiority of the combination gemcitabine and cisplatin over gemcitabine alone, resulting in a median overall survival (mOS) of 11.7 months (95% confidence interval [CI]: 9.5–14.3) compared to 8.1 months (95% CI: 7.1–8.7) and median progression-free survival (mPFS) of 8 months (95% CI: 6.6–8.6) compared to 5 months (95% CI: 6.6–8.6) favouring the combination.[1] The ABC-02 trial was an extension of this prior ABC-01 trial, and also showed an improved tumour control rate with the same combination regimen compared to gemcitabine alone.[2]

The adverse events reported in the ABC-02 trial were comparable between the two treatment groups, except for liver function, which was worse in the gemcitabine alone group (27.1%) than in the combination group (16.7%). This might be explained by improved disease control in the combination group, allowing better biliary drainage. In the real-world clinic, the combination regimen seems generally well tolerated by patients.

Other chemotherapy doublets (e.g., capecitabine + cisplatin, gemcitabine + oxaliplatin) failed to improve outcomes compared to gemcitabine plus cisplatin.[3,4] While triplet chemotherapy regimens (e.g., mFOLFIRINOX [oxaliplatin + leucovorin + irinotecan + fluorouracil], gemcitabine + albumin-bound paclitaxel + gemcitabine, GEMOX [gemcitabine+ oxaliplatin] + capecitabine) showed better response rates compared to gemcitabine plus cisplatin, it did not translate into statistically significant improvement in OS.[5-7] Gemcitabine and cisplatin remained the standard of care for over a decade until the practice-changing TOPAZ-1 trial.

Combination Chemotherapy with an Immune Checkpoint Inhibitor (ICI)

TOPAZ-1 was a double-blind, placebo-controlled randomized Phase III trial investigating the addition of durvalumab to the gemcitabine and cisplatin combination.[8] A total of 685 patients who had previously untreated or recurrent metastatic or unresectable advanced BTC were randomly assigned to receive either durvalumab or placebo with gemcitabine and cisplatin for eight cycles, followed by maintenance durvalumab or placebo. The study showed an improvement in median OS with the durvalumab

chemotherapy combination having an OS of 12.8 months (95% CI: 11.1–14.0) compared to 11.5 months (95% CI: 10.1–12.5) for the chemotherapy plus placebo group (hazard ratio [HR]: 0.80; 95% CI: 0.66–0.97; P=0.021). The PFS also improved with a median PFS of 7.2 months (95% CI: 6.7–7.4) for the durvalumab combination group, compared to 5.7 months (95% CI: 5.6–6.7) for the placebo group.

The outcomes in this study were observed to be better and more pronounced with treatment beyond six months. The estimated OS rate at 24 months was 24.9% (95% CI: 17.9–32.5) for the durvalumab group compared to 10.4% (95% CI: 4.7–18.8) for the placebo group. No increased toxicity was reported using the durvalumab plus chemotherapy combination, with comparable rates of Grade 3 or 4 adverse events in both groups (75.7% vs. 77.8% for the durvalumab and the placebo group, respectively). The addition of immunotherapy was tolerable, with Grade 3/4 immune-related adverse events reported as 2.4% in the chemotherapy plus durvalumab arm.

The Phase III KEYNOTE-966 trial had a similar design but enrolled more patients (N=1069).[9] Patients with unresectable locally advanced or metastatic BTC were randomized to receive either pembrolizumab or placebo in combination with gemcitabine and cisplatin for 8 cycles, followed by maintenance gemcitabine combined with pembrolizumab or placebo. The median OS was longer in the pembrolizumab group, at 12.7 months (95% CI: 11.5–13.6) compared to 10.9 months (95% CI: 9.9–11.6) in the placebo group (HR: 0.83 [95% CI: 0.72–0.95]) with estimated OS rates at 24 months of 25% (95% CI: 21–29) and 18% (95% CI: 15–22) for the pembrolizumab and the placebo group, respectively. The median PFS in the pembrolizumab group was 6.5 months (95% CI: 5.7–6.9) compared to 5.6 months (95% CI: 5.1–6.6) in the placebo group.

Therefore, the TOPAZ-1 and KEYNOTE-966 studies showed improved outcomes using a combination of an ICI with the standard of care chemotherapy, making their way to become the first-line treatment choice in advanced or metastatic BTC. These combination regimens had an acceptable safety profile, with comparable results in Grade 3 or 4 adverse events in TOPAZ-1 and KEYNOTE-966 (75.7% vs. 77.8%) and (79% vs. 75%), respectively.

Targeted Therapy

Next-generation sequencing (NGS) has improved our understanding of the BTC molecular profile. Various mutations, amplifications, and gene alterations have been described in BTC, with varying incidence in each tumour subtype reflecting their different etiology (**Figure 1**). The therapeutic implications of some of these alterations were established using targeted therapy in different studies over the last decade.

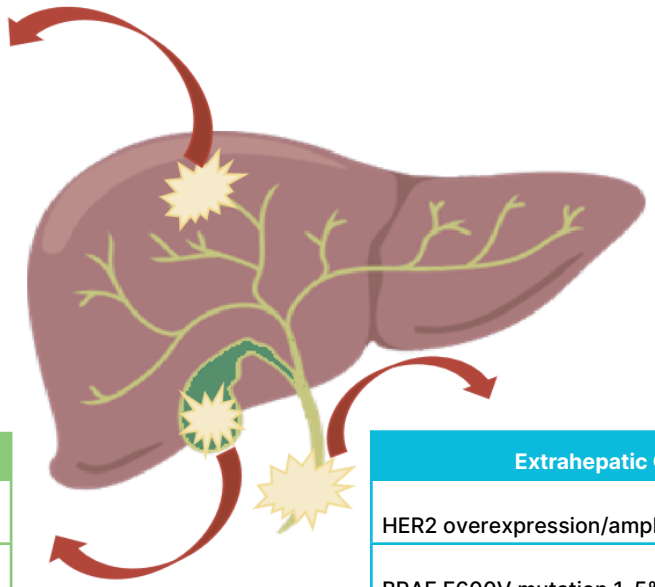
The incidence of high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) in BTC is low, ranging between 1% and 3%, and can be either hereditary, as in Lynch Syndrome-associated tumours, or sporadic.[10,11] Testing for MSI-H/dMMR has gained interest for almost all solid tumours as a useful predictor of response to ICI.[12] In the Phase II trial KEYNOTE-158, the use of pembrolizumab in patients with MSI-H/dMMR solid tumours (non-colorectal) resulted in a clinically meaningful mOS of 20.1 months (95% CI: 14.1–27.1).[13] The objective response rate (ORR) was 30.8% (95% CI: 25.8%–36.2%) with a median duration of response of 47.5 months. This study enrolled 351 patients, of whom 22 (6.3%) had BTC.

Dostarlimab is another ICI monoclonal antibody that inhibits the programmed cell death 1 receptor (PD-1) and has shown proven clinical activity in MSI-H/dMMR solid tumours. In the Phase I multicenter GARNET trial with 327 patients enrolled, of which 10 patients (3.1%) had BTC, dostarlimab had an ORR of 44.0% (95% CI: 38.6%–49.6%), with 72.2% of the responders having a lasting response for 12 months or longer.[14]

With the approval of gemcitabine and cisplatin plus ICI in advanced or unresectable BTC, ICI is available for rare cases of MSI-H/dMMR BTC. ICI is considered standard practice in these patients, provided there is no contraindication to immunotherapy. No studies have compared chemotherapy plus ICI versus ICI alone in this patient population. However, in clinical scenarios where chemotherapy toxicity occurs, we recommend discontinuing chemotherapy and continuing ICI monotherapy.

Human epidermal growth factor receptor 2 (HER2), is a membrane tyrosine kinase receptor protein that is known to promote cell growth and proliferation in various cancer types when overexpressed or amplified. In BTC HER 2 is more prevalent in Gallbladder Cancer with reported incidence 15–30%, compared to 10–20% in

Intrahepatic CCA
IDH1 mutation 10–20%
FGFR2 fusion/rearrangement 9–15%
HER2 overexpression/amplification 5–20%
BRAF E600V mutation 1–5%
MSI-H/dMMR 1–3%
NTRK fusion <1%
RET fusion <1%



Gallbladder CA
HER2 overexpression/amplification 15–30%
BRAF E600V mutation 1–5%
MSI-H/dMMR 1–3%
NTRK fusion <1%
RET fusion <1%

Extrahepatic CCA
HER2 overexpression/amplification 5–20%
BRAF E600V mutation 1–5%
MSI-H/dMMR 1–3%
FGFR2 fusion/rearrangement rare
IDH1 mutation rare
NTRK fusion <1%
RET fusion <1%

Figure 1. Mutations, amplifications, and gene alterations in biliary tract cancer. Varying incidence in each tumour subtype reflects their different etiology; *courtesy of Arwa Ahmed Abdelrahim, MD, and Rachel Goodwin, MD.*

Abbreviations: CA: carcinoma; **CCA:** choriocarcinoma; **dMMR:** deficient in mismatch repair; **FGFR:** fibroblast growth factor receptor; **HER2:** receptor tyrosine-protein kinase erbB-2; **IDH:** isocitrate dehydrogenase; **MSI-H:** high microsatellite instability; **NTRK:** neurotrophic tyrosine kinase receptors.

extrahepatic cholangiocarcinoma (ECC) and 3–5% in intrahepatic cholangiocarcinoma (ICC).[15] Over the years, there is cumulative evidence showing clinical activity of targeting HER2 in BTC with different agents mostly after progressing on one or more lines of therapy. Zanidatamab is a bispecific humanized monoclonal antibody that inhibits the HER2 protein via two different domains with proven clinical activity in BTC after progressing on Gemcitabine based chemotherapy.[16] HERIZON BTC-302 is an ongoing randomized phase 3 clinical trial investigating the addition of Zanidatamab to the first line standard of care therapy Gemcitabine and Cisplatin with or without ICI in HER2 positive advanced BTC.[17] The trial is looking at efficacy and safety of Zanidatamab in the first line treatment setting with PFS as the primary end point in HER2 positive IHC +3 patients. This is the first phase 3 clinical trial addressing integrating molecular alterations in the first line therapy in BTC and the results may shape the treatment for this subset of patients.

Treatment Selection

First-line Treatment

The selection of first-line treatment in advanced or metastatic BTC tumours with proficient or unknown MMR status depends on many factors, such as the drug availability/coverage, patient's performance status, concurrent medical conditions (e.g., contraindication to immunotherapy), and past medical history. In Canada, for patients with advanced BTC without contraindications to ICI, gemcitabine and cisplatin plus ICI is the standard of care for first-line treatment. A Health Canada indication for chemotherapy plus durvalumab was announced in 2022, followed by chemotherapy plus pembrolizumab in 2023. Clinical guidelines quote the use of either durvalumab or pembrolizumab in combination with chemotherapy as an acceptable option.[18] Both drugs are given with the same chemotherapy regimen for 8 cycles followed by maintenance either alone (durvalumab) or combined with gemcitabine (pembrolizumab). The decision to continue maintenance gemcitabine + ICI depends on many factors, including the patient's chemotherapy side effects, such as myelosuppression, performance status, and ability to tolerate two systemic therapy drugs, and willingness to come to the cancer centre every 3 weeks versus every 4 weeks for infusions. A pro-con discussion can aid in this decision.

The chemotherapy combination of gemcitabine and cisplatin without ICI remains a first-line option for advanced BTC. In the TOPAZ-1 trial,18% of patients reported a partial response on the placebo arm and 0.6% had a complete response. Chemotherapy alone is an appropriate choice for patients who have a contraindication to ICI, for example, in patients with an organ transplant, moderate to severe autoimmune disease, or previous severe ICI-related toxicity. Carboplatin can be used as a substitute for cisplatin if toxicity requires. Single-agent gemcitabine is recommended for patients who are not candidates for doublet chemotherapy regimens due to poor performance status.

Later Lines of Treatment

After the first-line treatment, patients with progressive BTC have poor survival outcomes, and the chance to receive second-line therapy is limited to patients with a good performance status. No standard second-line treatment exists for advanced or metastatic BTC; however, fluorouracil-based chemotherapy is usually used in this scenario after progression on a gemcitabine combination.

FOLFOX chemotherapy became a widely accepted treatment option after the Phase III ABC-06 trial that showed improvement in OS when adding second-line FOLFOX to active symptom control compared to only active symptom control, resulting in an OS of 6.2 months vs. 5.3 months, with a 12-month OS rate of 25.9% vs. 11.4%, respectively.[19] Other treatment regimens can also be used, including FOLFIRI (leucovorin, fluorouracil, irinotecan) and the tyrosine kinase inhibitor regorafenib.[20,21]

Targeted therapy can be more effective compared to chemotherapy. Many studies have shown clinical anti-tumour activity of drugs targeting molecular alterations in advanced BTC in the second-line and beyond. Identifying the tumour molecular profile using genomic sequencing or NGS is best performed early upon presentation with advanced disease. Availability and funding for the tests and drugs are the main obstacles that steer the treatment selection process away from or toward a specific therapy. We have summarized the targetable molecular alterations in BTC and the relevant studies with targeted therapies in **Table 1**.

Future Directions

The most significant advancement in the first-line BTC treatment has been the addition of ICI to the standard chemotherapy regimen of gemcitabine and cisplatin. However, biomarkers that predict which patients will gain the greatest benefit from immunotherapy remain lacking.

BTC are still treated collectively as one disease, although the advances in genomic studies have shown that they may not only have a different anatomical location, but they may also exhibit different genetic alterations governing the pathogenesis of each disease subtype. This highlights the importance of studies focusing on moving targeted therapies to the first-line setting.

Biomarker	Drug	Trial	Phase	Tumour type	Line	N	Primary endpoint
***IDH1* mutation**	Ivosidenib	ClarIDHy[22,23]	III	CCA	2nd or 3rd	185	mPFS: 2–7 months
***FGFR2* rearrangement/fusion**	Pemigatinib	FIGHT-202[24]	II	CCA	2nd or more	107	ORR: 35.5%
	Futibatinib	FOENIX-CCA2[25]	II	iCCA	2nd or more	103	ORR: 42%
***HER2neu* overexpression/ amplification**	Pertuzumab + trastuzumab	MyPathway[26]	IIa	BTC	2nd or more	39	ORR: 23%
	Zanidatamab	HERIZON-BTC-01[16]	IIb	BTC	2nd	80	ORR: 41.3%
	Tucatinib + trastuzumab	SGNTUC-019[27]	II	BTC cohort	2nd or more	30	ORR: 46.7%
	Trastuzumab deruxtecan	HERB[28]	II	BTC	2nd	22	ORR: 36.4%
***NTRK* fusion**	Entrectinib	STARTRK-2[29]	II	Basket trial	Any line	155	ORR: 61.3%
	Larotrectinib	NAVIGATE[30]	I/II	Basket trial	Any line	55	ORR: 75%
***RET* fusion**	Pralsetinib	ARROW[31]	I/II	Basket trial	Any line	29	ORR: 57%
***BRAF* V600E**	Dabrafenib + trametinib	ROAR[32]	II	BTC cohort	2nd or more	43	ORR: 47%

Table 1. Targetable molecular alterations in biliary tract cancer and pivotal studies; *courtesy of Arwa Ahmed Abdelrahim, MD, and Rachel Goodwin, MD.*

Abbreviations: FGFR: fibroblast growth factor receptor; **HER2:** receptor tyrosine-protein kinase erbB-2; **IDH:** isocitrate dehydrogenase; **mPFS:** median progression-free survival; **NTRK:** neurotrophic tyrosine kinase receptor; **ORR:** objective response rate.

Circulating tumour DNA (ctDNA) assessment is an emerging technique that is now widely used for different solid tumour studies and has the potential to overcome tumour heterogeneity. In BTC, ctDNA can be used to identify arising oncogenic drivers responsible for the acquired resistance to chemotherapy or targeted therapy or can be used to identify genetic alterations to help inform treatment selection. In a comprehensive study that looked at cell-free DNA (cfDNA), which combines ctDNA and circulating tumour cells (CTC), in samples from 1,671 patients with advanced BTC, actionable genetic alterations were detected in 44% of patients.[33] This analysis reported the concordance between cfDNA and tissue for detecting mutations was high for *IDH1* mutations (87%) and the *BRAF* V600E mutation (100%), while it was low for detecting *FGFR2* fusions (18%). These correlation studies are critical given that obtaining adequate tissue from locally advanced, non-surgical patients is often challenging.

Conclusion

Advancing the treatment of BTC remains an unmet need among solid tumours. With the addition of ICI to chemotherapy in recent years, meaningful improvement has been observed in the treatment of advanced BTC, putting durvalumab and pembrolizumab as equally effective additions to chemotherapy.

The advances in molecular profile assessment not only improved our understanding of the different disease subtypes but also paved the way to explore targeted therapies, adding more treatment options after progression on first-line treatment. The treatment selection is more challenging beyond the first-line, and is dictated by actionable genomic alterations, performance status, patient's preferences, availability, and cost.

Recognizing the importance of molecular testing, Canadian Cholangiocarcinoma Collaborative (C3) has supported a Canadian testing program to improve accessibility of patients to these tests. In addition, C3 has expert tumour board meetings with the goal of discussing treatment selection, educating on identified molecular alterations, and reviewing access to clinical trials.

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