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Second-line Treatment Strategies in Biliary Tract Cancers

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Introduction

Biliary tract cancers (BTCs) are a highly heterogenous group of tumours arising from the bile ducts (cholangiocarcinoma [CCA]) and gallbladder. Of note, tumours of the ampulla of Vater typically fall under this definition but tend to be excluded from second-line treatment studies. Cholangiocarcinomas are further classified into intrahepatic (iCCA, including hilar) and extrahepatic (eCCA). Together, they account for approximately 15% of primary liver cancers and 3% of all gastrointestinal malignancies.[1] However, iCCA and eCCA are separate entities that differ in incidence, clinical presentation, natural evolution, and molecular profile. Specifically, iCCA is less commonly associated with biliary obstructive symptoms and thus tends to be diagnosed incidentally and at a more advanced stage than eCCA.[2] The diagnostic challenges partly stem from the localization of these tumours, deep in the hepatic and biliary systems, where it is often difficult to obtain a tissue biopsy or an adequate aspiration cytology. iCCA can be misclassified as carcinoma of unknown primary (CUP) as histologically it can be impossible to distinguish from metastatic adenocarcinoma of an extrahepatic primary tumour, and the primary tumour can be small and not well identified on imaging.

The unique features of these tumours may in part explain their poor prognosis. Overall, the 5-year survival rate of CCA is estimated to be less than 25% for all stages combined, reflecting a very modest treatment effect.[1] Chemoimmunotherapy combinations are now globally accepted as the standard first-line treatment, but uncertainties remain regarding second and later lines of treatment. This review will summarize the available treatments beyond the first line with a focus on the emerging field of molecular precision medicine.

First-line Standard of Care

The ABC-02 trial has established the chemotherapy standard of care for first-line treatment of locally advanced or metastatic BTCs. The gemcitabine and cisplatin (GC) combination (8 cycles) showed a significant survival advantage compared to gemcitabine alone (6 cycles) with a median progression-free survival (PFS) of 8.0 months vs. 5.0 months ($p < 0.001$), and a median overall survival (OS) of 11.7 months vs. 8.1 months ($p < 0.001$).[3]

More recently, two trials have confirmed the added benefit of immunotherapy to this chemotherapy backbone. The TOPAZ-01 trial confirmed the superiority of the addition of durvalumab (programmed cell death ligand 1 [PD-L1] inhibitor) to GC with a median OS of 12.9 months (95% confidence interval [CI]: 11.6–14.1) vs. 11.3 months (95% CI: 10.1-12.5) in the placebo and GC groups, respectively (hazard ratio [HR]: 0.76, 95% CI: 0.64-0.91).[4] The KEYNOTE-966 trial yielded similar results with the combination of pembrolizumab (programmed cell death protein 1 [PD-1] inhibitor) and GC with a median OS of 12.7 months (95% CI: 11.5–13.6) vs. 10.9 months (95% CI: 9.9–11.6) in the placebo and GC group, respectively (HR: 0.83, 95% CI: 0.72–0.95).[5] To date, no biomarkers have been confirmed for patient selection.

Therefore, in the absence of contraindication to immunotherapy, the addition of either durvalumab or pembrolizumab to GC represents the new standard of care for patients with previously untreated metastatic or unresectable BTCs.

Second-line Therapy and Beyond

Chemotherapy for Unselected Groups

Until 2019, the role of second-line chemotherapy after progression on GC was unclear with retrospective studies suggesting a benefit only in patients with a good performance status. Some retrospective series and systematic reviews suggested that around 30-40% of patients would be fit enough for this treatment.[6] However, it has been estimated that only 15-25% of patients went on to receive second-line therapy.[7]

Although the advent of molecular precision medicine has led to the development of new targeted therapies, more than half of CCAs do not express any actionable mutations. For those patients, second-line treatment comprises chemotherapy either as a combination or single agent. Several different chemotherapy agents have been used based on phase II or retrospective trials, including fluoropyrimidine, irinotecan, docetaxel, gemcitabine, and platinum-based compounds.[7-13]

Folinic Acid, Fluorouracil, and Oxaliplatin (FOLFOX)

The pivotal ABC-06 trial was the first prospective, adequately powered, randomized trial showing a survival benefit for FOLFOX compared to active symptom control alone (median OS: 6.2 months vs. 5.3 months). At 12 months, the OS rate was more than doubled with chemotherapy (25.9% vs. 11.4%).[7] Results of quality of life (QoL) analyses presented at the European Society for Medical Oncology (ESMO) congress in 2022 showed that FOLFOX allowed stabilized QoL and helped avoid worsening nausea and pain.[8] This regimen is considered the standard of care second-line option for unselected patients in the absence of a targeted therapy with better outcomes. Notably, the benefit of single agent fluoropyrimidine compared to doublet therapy remains unknown.

Folinic Acid, Fluorouracil, and Irinotecan (FOLFIRI)

The NIFTY trial was a promising phase II study evaluating nano-liposomal irinotecan (nal-IRI) and 5-fluorouracil (5-FU) compared to 5-FU alone after progression on GC. Conducted exclusively in South Korea, the study showed a median PFS of 4.2 months for the combination vs. 1.7 months with 5-FU alone. The 6-month PFS rates were 31.8% vs.15.1%, respectively.[9] A second phase II study conducted in Korea failed to demonstrate superiority of modified formulations of FOLFIRI to FOLFOX (mFOLFIRI to mFOLFOX) with 6-month OS of 44.1% vs. 54.1%, respectively. Both regimens, however, appeared to have similar antitumour activity in terms of objective response rate (ORR) and disease control rate (DCR) (4.0% and 64.0%, respectively, with mFOLFIRI vs. 5.9% and 66.7% with mFOLFOX).[10] In the absence of confirmatory studies in a Western population, FOLFIRI is considered as a reasonable alternative option to FOLFOX, for example if oxaliplatin is contraindicated.[11]

Capecitabine/5-FU

The benefit of a fluoropyrimidine-platinum combination therapy compared to fluoropyrimidine alone has been inconsistent between studies. A 2017 retrospective study of 748 patients from Korea showed that the combination was associated with higher response rates than monotherapy (8% vs. 1%) after failure of GC, but this did not translate into significant improvements in PFS (median 2.6 vs. 1.8 months) or OS (median 6.2 vs 6.5 months).[12] Another retrospective study of 325 patients treated at BC Cancer from 2009 to 2015 also seemed to support the use of single-agent capecitabine following failure of first-line treatment. Notably, the included cohort was obtained prior to the ABC-06 trial: capecitabine was the most used regimen (30%), followed by FOLFIRI (17%), and 5-FU monotherapy (15%). The median OS was prolonged for all patients who received second-line chemotherapy as compared to patients who only received first-line chemotherapy (17.3 months vs. 9.5 months), regardless of the second-line regimen used.[13]

No randomized trials have been conducted to assess the value of systemic treatment in advanced CCA without an actionable mutation beyond second line.[6]

Precision Medicine and Targeted Therapies

Research in molecular profiling techniques and precision medicine has led to a better understanding of the driving mechanisms behind the oncogenesis of BTCs. Through DNA next-generation sequencing (NGS) and RNA sequencing (RNAseq), multiple tumour gene alterations have been identified in this cancer type, for which targeted therapies may be available. It is estimated

that up to 40% of CCA have actionable targets with different frequencies in iCCA, eCCA, and gallbladder carcinoma (GBC).[14] Of the alterations with data supporting the use of targeted drugs, the most frequent are rearrangements and fusions of the fibroblast growth factor receptor 2 (*FGFR2*) in iCCA, mutations of the genes encoding isocitrate dehydrogenases 1 and 2 (*IDH1, IDH2*) in iCCA, amplification and/or overexpression of the *ERBB2* gene encoding the protein HER2 (in GBC > eCCA > iCCA) **(see Figure 1)**. Other alterations, such as the presence of microsatellite instability (GBC), *BRAF* V600E mutation (GBC), *KRAS* G12C, and *NTRK* fusion are less frequent. **Table 1** summarizes the current available options for each that will be discussed in this article.

FGFR

FGFR2 fusions or rearrangements are observed in 10-20% of CCAs, almost exclusively in iCCA. First-generation FGFR inhibitors are non-selective tyrosine kinase inhibitors. Their broad effects on multiple receptor tyrosine kinases (RTKs) are thus accompanied by a challenging toxicity profile, which has led to the development of second-generation pan-FGFR inhibitors.[16] The main second-generation molecules and their respective phase II trials are summarized in **Table 2**.

One of the largest trials with pemigatinib included patients with unresectable or metastatic CCA (predominantly iCCA) having received at least one previous treatment. Patients were pre-screened centrally for *FGF/FGFR* status using DNA sequencing (including patients with a previous *FGF/FGFR* status report based on local assessment) and assigned to one of three cohorts: (A) *FGFR2* fusions or rearrangements, (B) other *FGF/FGFR* alterations, or (C) no *FGF/FGFR* alterations. Of 1,206 patients that were pre-screened (and 85 included from a previous report), 146 patients were enrolled, the vast majority in cohort A (107 patients). In this cohort, 35.5% achieved an objective response (three complete responses and 35 partial responses; 95% CI: 26.5-45.4) with a DCR of 82%. Although not mature at the data cut-off, median PFS was 6.9 months (95% CI: 6.2-9.6) and median OS 21.1 months (95% CI:

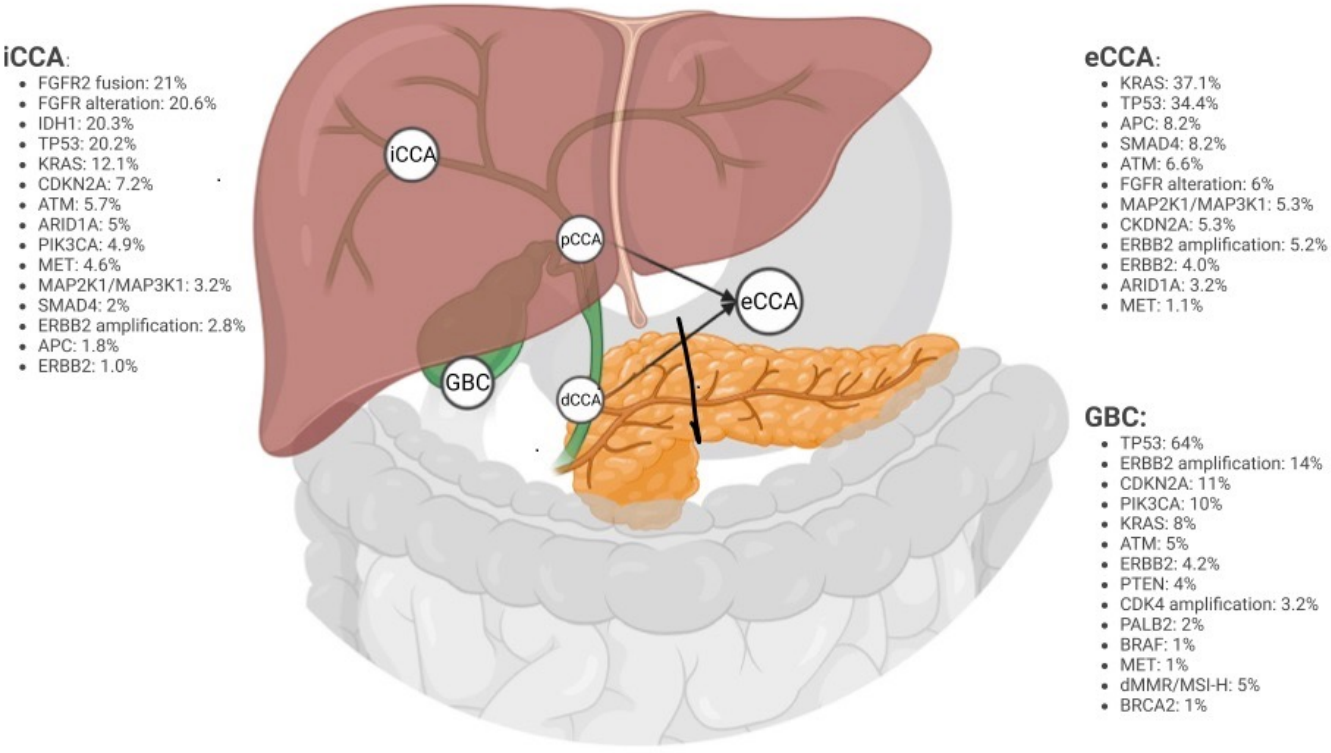

Figure 1. Biliary tract cancer molecular alteration prevalence by subtype[15]; *courtesy of Giulia Pool, MD, and Janine M. Davies, MD, BN, MSc, FRCPC.*

Abbreviations: 1L: eCCA: extrahepatic cholangiocarcinoma; **GBC:** gallbladder carcinoma; **iCCA:** intrahepatic cholangiocarcinoma.

Target	Molecule
FGFR	Pemigatinib Infigratinib Derazantinib
IDH1	Ivosidenib
Her2	Trastuzumab, pertuzumab Zanidatamab Neratinib
NTRK	Larotrectinih Entrectinib
BRAF	Dabrafenib, trametinib

Table 1. Precision oncology options for biliary tracts cancers; *courtesy of Giulia Pool, MD, and Janine M. Davies, MD, BN, MSc, FRCPC.*

14.8- not estimable [NE]).[17] The results for cohort B and cohort C were less promising but included a very small number of patients (20 and 18 patients, respectively). Trials of infigratinib and derazantinib are less mature but show lower response rates and similar mPFS.[18]

The adverse events associated with these agents are similar as a class, and overall, well tolerated. They include hyperphosphatemia, stomatitis, diarrhea, hand-foot syndrome, and fatigue. Hyperphosphatemia can, however, be quite serious, requiring serial serum phosphate monitoring, low-phosphorus dietary modifications, phosphate binders or phosphaturic agents, and sometimes dose reductions. Retinopathy is another serious potential complication, most associated with erdafitinib.[16]

Together, these promising results have led to several ongoing trials assessing FGFR inhibitors in the first-line setting. Another active focus of research is understanding the resistance mechanisms to these agents, both for the primary refractory patients and those with acquired resistance. For example, in a phase I study of the third-generation FGFR inhibitor futibatinib, approximately one third of patients had previously received FGFR inhibitors, mostly ATP-competitive inhibitors such as pemigatinib. Of these patients, 17.9% still experienced objective responses[20], suggesting a potential benefit of sequential treatment strategies in FGFR2-altered CCAs beyond the second line.

IDH1/2

Somatic point mutations in *IDH1* and *IDH2* genes have been associated with the production and accumulation of the onco-metabolite D2-hydroxyglutarate (D-2HG) that leads to epigenetic changes, impaired DNA repair, and aberrant cell metabolism, promoting tumourigenesis. *IDH1* mutations are detected in approximately 15-20%

	Trial	Phase and study design	Population (treatment line)	Primary objectives	Results		
					ORR	mPFS	mOS
Pemigatinib	FIGHT-202[17]	Single-arm multicentre phase II	n = 147 (L2+)	ORR	Cohort fusion: 35.5%	6.9 months	21.1 months
Infigratinib	CBGJ398X2204[18]	Single-arm multicentre phase II	n = 61 (L2+)	ORR	14.8%	5.8 months	N/A
Derazantinib	FIDES-01[19]	Single-arm multicentre phase II	n = 28 (L2+)	mPFS	Best overall response 8.7%	7.3 months	N/A

Table 2. Published studies evaluating targeted therapies against *FGFR* fusions; *courtesy of Giulia Pool, MD, and Janine M. Davies, MD, BN, MSc, FRCPC.*

Abbreviations: mOS: median overall survival; **mPFS:** median progression-free survival; **N/A:** not available; **ORR:** objective response rate.

of iCCA, compared to 0.8% of eCCA. Only one *IDH-1* inhibitor, ivosidenib, has been tested in a phase III trial for patients with *IDH1*-mutated CCA who progressed on up to two previous treatment regimens for advanced disease. Of the 230 patients screened, 187 were randomized (2:1) to receive either ivosidenib or placebo. More than 90% of the patients had iCCA and approximately 55% had received only one prior line of therapy. The PFS was significantly improved with ivosidenib (4 months) compared with placebo (2.7 months). The benefit in median OS was not statistically significant, possibly due to a high rate of crossover between the two groups. The treatment appeared to be well tolerated, the most common treatment-related adverse events being nausea (35%), diarrhea (31%), and fatigue (26%).[21] Many other IDH-mutant inhibitors and IDH pathway target therapies are currently under investigation in clinical trials.

HER2

Alterations of the *ERRB2* or HER2/Neu gene include amplifications, overexpression, or more rarely mutations. HER2 amplification is more prevalent in eCCA and gallbladder cancer (5%-15%) but is also observed in iCCA. Although no phase III trials have been published for this subset of patients, there is an undeniable interest in developing new strategies in HER2-amplified CCA.

The MyPathway phase IIa multiple basket study is an ongoing trial investigating pertuzumab plus trastuzumab in patients with HER2-positive advanced biliary tract cancer after at least one previous line of treatment. Patients were enrolled based on HER2-positive archival or fresh tumour tissue samples. At the March 10, 2020 cut-off, 661 patients were enrolled, including 39 patients with a HER2-positive BTC (90% had HER2 amplification without overexpression or overexpression status unknown). The ORR for this treatment regimen was 23%, the DCR 51%, median PFS was 4.0 months, and median OS was 10.9 months.[22] While the results are preliminary, they support a potential new application for these anti-HER2 therapies already included in guidelines for other cancer types with HER2 positivity.

New agents are also being investigated, such as zanidatamab, a bispecific antibody targeting two distinct HER2 epitopes. The HERIZON-BTC-01 phase IIb trial yielded promising results with zanidatamab monotherapy (ORR: 41.3%, DCR: 68.8%, median PFS: 5 months) for patients who progressed on previous gemcitabine-based therapy. The trial is ongoing but now closed to recruitment. The toxicity profile also appeared to be acceptable with the most common adverse events being diarrhea (32%), infusion-related reactions (32%), and decreased ejection fraction (6%).[23]

Targeting gene mutations rather than gene amplification may also have potential. The SUMMIT trial is an open-label, single-arm, multi-cohort, phase II, 'basket' trial investigating neratinib in patients with solid tumours harbouring oncogenic HER2 somatic mutations. In the BTC cohort, 25 treatment refractory patients were enrolled. The results were positive, although modest (ORR: 16%, median PFS: 2.8 months, OS: 5.4 months) reflecting the need to conduct further studies looking at combinations to improve the responses. However, the study has been terminated based on the sponsor's development plans for neratinib (and not based on any new efficacy or safety data for neratinib).[24]

Neurotrophic Tyrosine Receptor Kinase (NTRK)

Fusions of one of the three *NTRK* genes (1, 2, or 3) are rare alterations in BTCs (<1%). However, small trials with NTRK inhibitors have shown high response rates and durable responses. Larotrectinib is a potent and highly selective small-molecule inhibitor of all three TRK proteins. A phase I/II trial of *TRK* fusion–positive cancers, with only 2 of 55 patients enrolled having CCA, reported an ORR of 75% with a 1-year PFS of 55% for all patients. Only one patient with CCA had a tumour response.[25]

Entrectinib is another NTRK1, 2, 3 inhibitor that has shown promising results. An integrated database comprising of datasets of three ongoing phase I or III clinical trials reported the results in a population of 54 adults with advanced or metastatic *NTRK* fusion-positive tumours (only 1 CCA). Nevertheless, that patient was among the responders, with an ORR of 57% and median PFS of 11.2 months.[26]

Both therapies appear to be safe with most treatment-related adverse events being grade 1-2 and reversible, such as increased alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) levels, fatigue, nausea/ vomiting, diarrhea, dizziness, and anemia.

BRAF

The *BRAF* gene encodes a serin/threonine protein kinase activating the MAP kinase/ERK

signaling pathway. Activating mutations have been described mainly in iCCA with a prevalence of 1-3%. The V600E mutation of the *BRAF* gene is particularly of interest because it is potentially targetable with dual inhibition of BRAF and MEK. The phase II ROAR basket trial investigated the combination of dabrafenib and trametinib in 8 cohorts of patients, including 43 patients with BTCs. The ORR was ≥50% across all cohorts (except high-grade gliomas). The median PFS was 9 months in the BTC cohort and OS was 13.5 months. The most reported adverse events were pyrexia (54.9%), fatigue (42.2%), and nausea (41.7%).[27]

KRAS

Although an activating mutation of the *KRAS* oncogene is found in 15-25% of BTC, only the KRASG12C mutation is accessible to pharmacological inhibition, which is present in 1% of CCAs. KRYSTAL-1 is a multicohort phase I/II study evaluating the KRASG12C selective and irreversible inhibitor adagrasib in patients with previously treated advanced solid tumours harbouring that mutation. A total of 42 patients were enrolled in this cohort, including 8 patients with BTCs. In a preliminary analysis, the reported ORR was 50% with a DCR of 100%. The most frequent adverse events were nausea (48%), diarrhea (43%), vomiting (43%) and fatigue (29%).[28] Although these treatments are not yet approved, inclusion of patients in clinical trials assessing adagrasib or sotorasib (another oral inhibitor specific for KRASG12C) is encouraged based on these results.

DNA Mismatch Repair Deficiency (dMMR) and/or Microsatellite Instability-high (MSI-H) Tumours

Beyond the first line combinations, immunotherapy has also been studied in BTCs, notably for patients with dMMR and/or MSI-H tumours, which account for 1-3% of all CCAs. The phase II KEYNOTE-158 trial enrolled 233 patients with previously treated advanced cancers from 27 non-colorectal tumour types, including 22 patients (9.4%) with MSI-H/dMMR CCAs with either somatic or germline MSI mutations. Of note, prior anti-PD-1 and anti-PD-L1 treatment were exclusion criteria for this study. Among CCAs, the ORR was 40.9%, PFS was 4.2 months, and OS was 24.3 months.[29]

In comparison, the role of immunotherapy in previously treated microsatellite stable (MSS)/proficient mismatch repair (pMMR) BTCs, especially after first-line immunotherapy, remains unclear. To date, trials have shown very modest benefits in this population of both single and dual agent immunotherapy.[10]

Other Immunotherapy Combinations with Kinase Inhibitors

Because of the disappointing results of immunotherapy alone in pMMR tumours, several trials have suggested a potential benefit of combining targeted small-molecule therapeutics with immune checkpoint inhibitors (ICIs) to increase their efficacy and produce more durable responses. One proposed strategy is to combine ICIs with anti-angiogenic therapies. The addition of the anti-angiogenic agent is thought to improve immunotherapy activity by contributing to lymphocyte cytotoxicity in the tumour microenvironment. The LEAP-005 trial evaluated the efficacy and safety of lenvatinib and pembrolizumab in patients with previously treated advanced solid tumours, including a BTC cohort of 31 patients. The results for that subgroup included an ORR of 10%, median PFS of 6.1 months, and median OS of 8.6 months.[30] Several trials investigating similar combinations of immunotherapy and anti-angiogenic therapies are ongoing. This could offer another option for previously treated advanced BTC without actionable mutations and help avoid chemotherapy-related toxicity.

Challenges in Molecular Testing

Despite the clear benefit of personalized medicine and molecular profiling, the clinical application of this strategy comes with several new challenges. One of the main issues is related to tissue sampling. Molecular profiling should be performed as early as possible, ideally at the initial diagnosis stage and early in treatment, to prevent later treatment delays. In some cases, sample testing may need to be repeated due to insufficient diagnostic tissue quality or quantity. This is especially true for iCCA, which is located deep in the hepatic and biliary system and difficult to access. Even for early stages of disease, it is important to consider preservation of tissue and sparing enough material to allow complimentary molecular analyses if recurrence occurs in the future. BTCs are aggressive tumours and patients tend to decline too rapidly to be eligible to start a second-line therapy, so any delay in testing

and delivering the results can thus have major consequences.[6]

Another challenge is related to the nature of each gene alteration and the specific testing that they might require. For example, NGS is used to detect mutations of genes such as *IDH1*, *BRAF*, and *KRAS*. The fusions or rearrangements of genes such as *FGFR2* or *NTRK* require RNAseq, which might not be included in all NGS panels. Although most NGS panels search for amplification/overexpression of *ERBB2* by studying the copy number variant of the gene, overexpression of HER2 protein is observed by immunohistochemistry (IHC) and requires confirmation by fluorescent *in situ* hybridization (FISH) when IHC overexpression is 2+.[31] MSI can be identified using DNA sequencing panels or through IHC staining of mismatch repair system (MMR) proteins to detect MMR deficiency.[6]

Another significant obstacle is the access and funding for these tests. Currently, there is no funded platform for molecular testing for patients in Canada. However, the Canadian Cholangiocarcinoma Collaborative (C3) works to facilitate patients' access to testing and identifying potential clinical trial opportunities.

ctDNA

Liquid biopsies refer to blood sampling meant to detect circulating tumour DNA (ctDNA), circulating cell-free RNA (ccfRNA), and cell-free DNA (cfDNA). This approach has gained popularity in cancer trials over the last decade for its diagnostic potential, and since it allows for molecular target selection, response monitoring, and resistance tracking.

A study evaluating the concordance between intrapatient ctDNA and tumour tissue mutations among 102 patients with BTC showed a sensitivity of 84.8% and positive predictive value of 79.4%. ctDNA analysis could identify targetable alterations in 34.3% of patients, including *FGFR2* fusions, *IDH1* mutations, MSI-H, and *ERBB2* amplifications.[32] In BTCs specifically, liquid biopsies may eventually provide an alternative to the challenging tissue-based analysis previously discussed.

A trial with futibatinib used genomic characterization of pre- and post-progression ctDNA to better understand patterns of resistance, ultimately showing that futibatinib was active against multiple *FGFR2* mutations that conferred resistance to earlier generations FGFR inhibitors.[33] ctDNA not only represents a useful tool at the time of diagnosis, but dynamic monitoring may also help predict the effect of therapy and identify the emergence of acquired resistance mutations during treatment. This may in turn help clinicians make treatment adjustments in a timely manner and provide a rationale for eventual sequential treatment strategies.[34]

Liquid biopsy has already proven effective in many other malignancies, but data on the application of ctDNA for BTC remains immature. Liquid biopsy can be considered for disease molecular profiling, but further research is warranted for its use in response monitoring and resistance tracking to ultimately optimize treatment strategies.

Conclusion

Cholangiocarcinomas are rare malignancies with an increasing incidence, especially for iCCA. Despite significant improvements associated with chemoimmunotherapy combinations in the advanced first-line setting, the prognosis remains extremely poor. The advent of personalized medicine has changed the treatment paradigm for many patients with advanced BTCs. As molecular profiling represents a new standard of care, it should be obtained early to tailor each patient's treatment. However, this remains a significant challenge in terms of access to both the molecular tests and the corresponding targeted agents. Because of the rarity of CCAs, most clinical trials include a small number of patients and are typically prospective/retrospective nonrandomized single-arm studies. More research is needed to optimize biomarker identification, patient selection, and the use of combination therapies to optimize treatment strategies.

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