Curr. Treat. Options in Oncol. (2020) 21: 63
DOI 10.1007/s11864-020-00767-3

Upper Gastrointestinal Cancers (JD Berlin, Section Editor)

New Treatment Options for Advanced Biliary Tract Cancer

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Published online: 29 June 2020

This article is part of the Topical Collection on *Upper Gastrointestinal Cancers*

Keywords Biliary tract cancer · Cholangiocarcinoma · Gall bladder cancer · Targeted therapy · Immunotherapy

Opinion statement

The standard of care first-line therapy for patients with advanced biliary tract cancers eligible for treatment continues to be the combination of gemcitabine and cisplatin. Based on the promising results of a phase II study, an ongoing multi-institutional phase III study is assessing the benefit of adding nab-paclitaxel to the chemotherapy doublet, and appropriate patients should be considered for enrollment at participating centers. We would recommend early comprehensive genomic profiling of patients' tumors to identify potentially targetable aberrations with available therapies. Results with therapeutic implications include tumors with microsatellite instability/deficient mismatch repair, alterations in *FGFR*, *IDH1/2*, and *HER-2*, and potentially other molecular vulnerabilities. Patients in whom a targetable genomic abnormality is found should be matched with appropriate agent. If a targetable fusion or mutation is not detected, patients eligible for second-line therapy should be considered for either clinical trial enrollment or a second-line cytotoxic chemotherapy regimen such as modified FOLFOX. Strategies incorporating immunotherapy into the treatment of patients with microsatellite stable advanced biliary tract cancers have yielded largely disappointing results thus far, and routine use of checkpoint inhibitors outside of a clinical trial is not recommended.

Introduction

Biliary tract cancers (BTCs) are a relatively rare group of malignancies comprised of intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, and gallbladder cancer (GBC). In 2019, over 12,000 individuals in the USA are expected to be diagnosed with almost 4000 patients expected to die from a BTC [1]. While the incidence of extrahepatic CCA has remained relatively stable over the past several decade, the incidence of intrahepatic CCA has continued to rise [2–5]. The reason for this increase in diagnosis remains unclear, although it may be related to changes in tumor classification and improved diagnostic techniques [3, 5]. Five-year survival for patients with distant disease is < 5% [6]. Whereas GBC is more common in females, both extrahepatic and intrahepatic CCA have a higher incidence in males [2, 7]. Because of its relative rarity and the heterogeneity of subtypes, few randomized prospective studies have been conducted to determine optimal treatment strategies for patients with advanced disease.

Chemotherapy

Cytotoxic chemotherapy was first demonstrated to improve overall survival (OS) for BTC patients in a prospective randomized in a study by Glimelius et al. in which patients with advanced pancreatic cancer and BTCs were treated with 5-fluoruracil (5-FU) + leucovorin ± etoposide compared with best supportive care [8]. Patients with BTCs treated with chemotherapy achieved a median OS of 6.5 months vs 2.5 months with best supportive care alone ($p = 0.1$). Subsequent phase II studies also demonstrated efficacy of gemcitabine and cisplatin-based chemotherapy regimens [9–12].

The current standard of care first-line treatment for advanced BTCs is combination gemcitabine and cisplatin. In the landmark ABC-02 study, this regimen was found to be superior to gemcitabine alone. In the trial, 410 patients with inoperable, advanced BTCs (including ampullary cancer) were randomized to either cisplatin 25 mg/m^2 + gemcitabine 1000 mg/m^2 on days 1 and 8 of every 3-week cycles or gemcitabine monotherapy dosed at 1000 mg/m^2 on days 1, 8, and 15 of every 4-week cycles. With a median follow-up of 8.2 months, the combination arm experienced a median OS of 11.7 months compared with 8.1 months in the monotherapy arm (hazard ratio [HR] 0.64; 95% confidence interval [CI], 0.52–0.80; $p < 0.001$). Rates of neutropenia were increased in the cisplatin-containing arm, but adverse effects were otherwise similar between the groups. Recently, efforts have been made to improve upon this standard of care. A phase II study of 60 patients evaluated the efficacy of the triplet gemcitabine, cisplatin, and nab-paclitaxel in patients with advanced BTCs [13•]. Median progression-free survival (PFS) and OS were 11.8 and 19.2 months, respectively, and the objective response rate (ORR) was 45%. Grade 3 and greater toxicities were observed in 57% of patients, with neutropenia the most common toxicity (32%). An ongoing multicenter randomized phase III Southwest Oncology Group study will be comparing first-line gemcitabine plus cisplatin with the doublet plus nab-paclitaxel (NCT03768414).

Data on chemotherapy options beyond first-line have historically been scarce. At the 2019 American Society of Clinical Oncology Annual Meeting, results from the multicenter phase III ABC-06 study were presented [14••]. This study randomized 162 patients with advanced BTCs previously treated with cisplatin + gemcitabine to either active symptom control (ASC) or ASC + modified 5-fluorouracil + oxaliplatin (mFOLFOX). Median OS was 6.2 months in the ASC + mFOLFOX arm compared with 5.3 months in the ASC alone arm with an improvement in 6 month OS rate from 35.5 to 50.6% with the addition of mFOLFOX. Smaller studies have demonstrated modest response rates in pre-treated patients with median PFS of largely 5-FU-based regimens in the 2 to 3 month range [15–17].

Targeted therapy

Similar to their anatomic and prognostic diversity, BTCs are genomically diverse. With the growing availability of molecular sequencing, recent studies have demonstrated the multitude of potentially actionable mutations harbored by BTCs, particularly in the case of intrahepatic CCA [18, 19]. In light of these findings, the most promising future for BTC treatment comes from the potential of targeted therapy for these tumors. Novel drugs that target the most frequently encountered aberrations in fibroblast growth factor receptor (*FGFR*), isocitrate dehydrogenase (*IDH*) 1 and 2, *BRAF*, and *HER2/neu* are beginning to change the treatment landscape for patients with BTCs [20•, 21•, 22, 23•, 24, 25] (Table 1).

IDH1 and IDH2

IDH1 and IDH2 are enzymes that play an important role in a number of cellular pathways including

metabolism and epigenetic regulation [26]. Previously most well described in gliomas, mutations in *IDH* have been identified in approximately 20% off intrahepatic CCAs and a much lower percentage of extrahepatic CCAs [19, 27]. AG-120 (ivosidenib) is an oral *IDH1* inhibitor that was initially studied in a phase I trial of patients with *IDH1*-mutant advanced solid tumors [28]. In the 73 patients with CCA included in the study, 4 (6%) patients had a partial response and 40 (56%) had stable disease. The 6-month PFS rate was 40% with 8 patients on treatment for greater than 1 year. The primary adverse effects were fatigue, nausea, vomiting, and diarrhea. The results of the international phase III ClarIDHy study were presented at the European Society for Medical Oncology 2019 Congress [29]. A total of 185 patients with mutant *IDH1* CCA were randomized 2:1 to ivosidenib vs placebo, 91% of whom had intrahepatic CCA. The primary endpoint was PFS which was improved with ivosidenib (HR 0.37; 95% CI, 0.25–0.54; $P < 0.001$). The ORR for ivosidenib was 2.4% with 50.8% achieving stable disease. Median OS was 10.8 months for ivosidenib compared with 9.7 months for placebo (HR 0.69), although 57% of placebo patients crossed over to receive ivosidenib. Nausea, diarrhea, and fatigue were the most common adverse effects, all of which occurred in > 20% of patients receiving ivosidenib. These promising results will likely lead to the approval of ivosidenib by the FDA for patients with CCA harboring *IDH1* mutations. AG-221 (enasidenib) is an oral inhibitor of the mutant *IDH2* enzyme, already approved for *IDH2*-mutant acute myeloid leukemia, and is currently being evaluated in a phase I/II study of patients with *IDH2*-mutant advanced solid tumors, including cholangiocarcinoma [30].

FGFR

The *FGFR* pathway is comprised of 4 transmembrane proteins (FGFR1, FGFR2, FGFR3, and FGFR4) and is intimately involved in cell proliferation, among other roles (NCT02273739). Fusions in the *FGFR2* gene have been reported in as many as 16% of intrahepatic CCAs, and appears to lead to a distinct clinical course that is more indolent than wild-type *FGFR2* CCAs [31–33]. Given the prevalence of *FGFR* pathway aberrations, multiple small molecule inhibitors have been developed in an effort to target this oncogenic driver. After promising activity was noted in a phase I study, an oral pan-*FGFR* inhibitor, BGJ398, was evaluated in a phase II study of 71 patients with advanced CCA harboring *FGFR2* fusions or other *FGFR* alterations who had progressed on prior therapy [21•, 34]. The updated results, presented at the ESMO 2018 Congress, demonstrated an ORR of 31.0% and a disease control rate of 83.6%, and responses were only seen in patients with *FGFR2* fusions [35]. The median PFS was 6.8 months (95% CI, 5.3–7.6 months), and BGJ398 was well tolerated with hyperphosphatemia as the most common adverse effect. Pemigatinib is also an oral pan-*FGFR* inhibitor which achieved an ORR of 35.5% in a phase II study of 107 patients with pre-treated cholangiocarcinoma with an *FGFR2* fusion [36]. The disease control rate was 82%, and the median PFS was 6.9 months (95% CI, 6.2–9.6 months). Development of acquired *FGFR2* gatekeeper mutations has already been described as a mechanism of adaptive resistance to *FGFR* inhibitors [37]. TAS-120 is a third-generation, irreversible *FGFR* inhibitor that may have a role in treating patients with acquired resistance to earlier generation *FGFR* inhibitors. Goyal et al. found that both BGJ398 and Debio 1347 were associated with their own spectrum of resistance mutations, most of which were able to be overcome with TAS-120 [23•]. With the projected surge in patients being treated with *FGFR* inhibitors, continued translational investigation into mechanisms and vulnerabilities of drug resistance will be of increasing importance.

EGFR/ERBB/BRAF

The epidermal growth factor receptor (EGFR) tyrosine kinase family includes the *ERBB1* (*EGFR*) and *ERBB2* (*HER-2/neu*) receptors. This is a pathway that has been implicated in oncogenesis in a number of solid tumors including breast, lung, and colon cancers. *HER-2* aberrations have been well described in BTCs, and, unlike *FGFR* and *IDH* mutations, occur less commonly in intrahepatic CCA [38]. In a retrospective review of 14 BTC patients with *HER-2* aberrations treated with *HER-2*-directed therapy, 9 of whom had gallbladder cancer, 8 patients achieved disease control, including one complete response [25]. A number of early phase studies are assessing the safety and efficacy of *HER-2*-targeted therapies in solid malignancies with *HER-2* over-expression, including BTCs (NCT03602079, NCT03330561, NCT02892123). *BRAF* and *MEK* are downstream proteins in the *MAPK* pathway, and targeting of these in patients with *BRAF* mutations has demonstrated efficacy in several solid tumors, most notably melanoma [39–

Table 1. Potentially targetable genomic alterations in biliary tract cancers

Alteration	Prevalence			Examples of agents under investigation
	ICC	ECC	GBC	
FGFR fusion	15–20%	< 5%	< 5%	Derazantinib (ARQ-087), Infigratinib (BGJ398), Erdafitinib, TAS-120, Pemigatinib, AZD4547
IDH1/2 mutation	~ 20%	< 5%	< 5%	Ivosidenib (AG-120), Enasidenib (AG-221), BAY-1436032, IDH305
ERBB2 (*HER-2*) amplification	< 5%	10–15%	10–20%	Trastuzumab, lapatinib, TAS0728, A166, PRS-343, ZW25
BRAF mutation	~ 5%	< 5%	~ 5%	Dabrafenib + trametinib
DNA damage repair gene mutation (*ARID1A*, *BRCA1/2*, etc.)	~ 25%	10–15%	~ 15%	PARP inhibitors: olaparib, rucaparib

ICC intrahepatic cholangiocarcinoma, *ECC* extrahepatic cholangiocarcinoma, *GBC* gallbladder cancer

43]. While rare, *BRAF V600E* mutations have been reported in BTCs, primarily intrahepatic CCA [44]. Thirty-three patients *BRAF V600E*–mutant BTCs were treated in the phase II basket trial, ROAR, with the *BRAF* and *MEK* inhibitors, dabrafenib and trametinib [45•]. The ORR in this cohort was 41% with a median PFS of 7.2 months (95% CI, 4.6–10.1 months). With the majority of the responding patients achieving at least 6 months of response, this represents another promising avenue for future therapeutic innovation.

Immunotherapy

Despite the success of immunotherapeutic approaches in the treatment of many advanced solid tumors, most patients with gastrointestinal cancers including BTCs have largely not benefited. Similar to the experiences in other gastrointestinal malignancies, the subset of patients who seem to respond to single agent checkpoint inhibition are those whose tumors are characterized by microsatellite instability (MSI-H) or deficient mismatch repair (MMR). Unfortunately, the percentage of BTC patients who are MSI-H is likely in the single digits [46, 47]. In the basket KEYNOTE-158 trial, 104 patients with advanced BTCs were treated with the PD-1 inhibitor, pembrolizumab, all of whom had proficient MMR and 61 of whom had PD-L1-positive tumors as defined in the study protocol [48]. In this cohort, the median PFS and OS were 2.0 and 9.1 months, respectively. The response rate was 5.8% with 16% of patients achieving stable disease as a best response. Twenty-four patients with BTCs were included in the KEYNOTE-028 trial which required PD-L1 positivity for enrollment [48]. In this group of patients, the median PFS and OS were 1.8 and 6.2 months, respectively. The response rate was 13.0%, and the median duration of response was not reached. The initial results of a phase II study assessing the combination of pembrolizumab and granulocyte macrophage colony-stimulating factor (GM-CSF) in 27 patients with advanced BTCs reported a promising 6-month PFS of 35% with a response rate of 19% [49]. Results of a randomized phase II trial of the PD-L1 inhibitor, atezolizumab, with or without the *MEK* inhibitor, cobimetinib, in advanced BTCs are eagerly awaited (NCT03201458).

Small studies have evaluated alternative immunotherapy strategies in patients with BTCs including vaccines and adoptive cell therapy. Eight patients with BTCs were included in a phase I study combining gemcitabine with a Wilms tumor protein 1 (WT1) vaccine, which provided 4 patients with stable disease at 2 months [50]. Mucin protein 1 (MUC1) is another antigen commonly found on BTCs, although a phase I study utilizing a MUC1 vaccine in BTC and pancreatic cancer patients demonstrated little efficacy [51].

Future directions

While the present landscape of approved and readily-available therapies for BTCs is largely dominated by cytotoxic chemotherapy, this is likely to soon change with the increasing access to targeted therapies. It will therefore be crucial for the subset of patients whose tumors do harbor genomic vulnerabilities to be studied longitudinally in order for researchers to identify mechanisms of adaptive therapeutic resistance. As mentioned

above, novel mutations in *FGFR2* have been identified in patients progressing on older generation *FGFR2* inhibitors, and these patients proceeded to benefit from third-generation *FGFR2* inhibitors such as TAS-120 [23•]. Harding et al. recently described isoform switching from *IDH1* to *IDH2* or vice versa as a mechanism of adaptive resistance to *IDH*-targeted therapies in 4 patients, one of whom had intrahepatic CCA [52].

Expanding the armamentarium of targeted therapies to exploit genomic susceptibilities in other BTCs is another important area of need. Currently, targetable mutations are less prevalent in patients with extrahepatic CCA and GBC compared with intrahepatic CCA. The success of inhibitors of Poly (ADP-ribose) polymerases (PARP) proteins in patients with other solid malignancies who harbor mutations in DNA repair genes has led to excitement about their use in BTCs. In a recent report of 422 patients with BTCs, genomic profiling identified that 12–15% of these patients had mutations in DNA repair genes, which including an expansive set of genes beyond just *BRCA1* and *BRCA2* [53]. Improving targeted therapies for patients with mutations in chromatin-modifying genes such as *ARID1A* and *BAP1*, aberrations found in up to 25% of patients with BTCs, is another area of active investigation [54]. Additionally, the development of pharmacologic agents that better target the KRAS-RAF-MEK-ERK, or PI3K-AKT-mTOR pathways could substantially increase the number of patients who could benefit from targeted therapies.

Conclusion

Cytotoxic chemotherapy continues to represent the mainstay of first-line treatment for patients with advanced BTCs, with combination gemcitabine + platinum as the preferred regimen. The results of the ongoing phase III SWOG S1815 study are eagerly awaited, assessing whether the triplet of gemcitabine + cisplatin + nab-paclitaxel improves upon the standard of care doublet. The recently reported results from the phase III ABC-06 study support the use of mFOLFOX in patients eligible for second-line chemotherapy. The most exciting avenue of therapeutic progress lies in expanding access to targeted therapy. Genomic sequencing of patients with BTCs, particularly in the case of intrahepatic CCA, should be performed early in the course of advanced disease in order to identify those patients who harbor targetable aberrations. Therapies targeting alterations in *FGFR*, *IDH1*, *IDH2*, and *HER-2/neu* hold promise for pushing the needle towards longer survival in this patient population. While immunotherapy has yet to make its mark on the field of BTCs, optimism remains that the correct combination or sequence of therapies may hold the key to expanding this therapeutic strategy to the majority of patients who do not have MSI-H tumors. Finally, expanding the arsenal of targeted therapies and increasing our understanding of mechanisms of therapeutic resistance represent some of the next breakthroughs that may improve outcomes for patients with advanced BTCs.

Compliance with Ethical Standards

Conflict of Interest

Jonathan D. Mizrahi declares that he has no conflict of interest.

Rachna T. Shroff has received research funding from Merck, Exelixis, Halozyme, Pieris, and Taiho, and has served as an advisory board member for Merck, Seattle Genetics, Exelixis, QED Therapeutics, Debiopharm, Agios, and Clovis Oncology.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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The recently reported results of BTC patients with BRAF V600E mutations treated with dual BRAF and MEK inhibition made a strong case for treating these patients with these therapies which have been very effective in BRAF-mutant melanoma patients.

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