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Paradigm shift of chemotherapy and systemic treatment for biliary tract cancer

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Abstract

Biliary tract cancers (BTC) are frequently identified at late stages and have a poor prognosis due to limited systemic treatment regimens. For more than a decade, the combination of gemcitabine and cis-platin has served as the first-line standard treatment. There are few choices for second-line chemo-therapy. Targeted treatment with fibroblast growth factor receptor 2 inhibitors, neurotrophic tyrosine receptor kinase inhibitors, and isocitrate dehydrogenase 1 inhibitors has had important results. Immune checkpoint inhibitors (ICI) such as pembrolizumab are only used in first-line treatment for microsatellite instability high patients. The TOPAZ-1 trial's outcome is encouraging, and there are several trials underway that might soon put targeted treatment and ICI combos into first-line options. Newer targets and agents for existing goals are being studied, which may represent a paradigm shift in BTC management. Due to a scarcity of targetable mutations and the higher toxicity profile of the current medications, the new category of drugs may occupy a significant role in BTC therapies.

Key Words: Biliary tract cancers; Gemcitabine and cisplatin combination; Fibroblast growth factor receptor 2 inhibitors; Isocitrate dehydrogenase 1 inhibitors; Neurotrophic tyrosine receptor kinase gene fusion inhibitors; Immune checkpoint inhibitors; Microsatellite instability high; Infragatinib; Pemigatinib

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Core Tip: There have been several developments in the field of advanced biliary tract cancer (BTC) therapy in recent years. First, the care of these hepatobiliary malignancies has improved as a result of better knowledge of the molecular basis of BTC. The Food and Drug Administration's approval of pemigatinib, infigratinib, and ivosidenib for fibroblast growth factor receptor 2-rearranged and isocitrate dehydrogenase 1-mutant cholangiocarcinoma illustrates the paradigm shift that the arrival of targeted agents has really brought about. Second, patients receiving modified fluorouracil, oxaliplatin, and liposomal irinotecan with fluorouracil-leucovorin, respectively, as second-line treatments after progressing to first-line cisplatin-gemcitabine, showed an overall survival advantage in the newly released Advanced Biliary Tract Cancer-06 and NIFTY studies.

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INTRODUCTION

The term "biliary tract cancers" (BTCs) refers to a group of aggressive and invasive hepatobiliary tumors that include ampulla of Vater cancer (AVC), gallbladder carcinoma (GBC), perihilar cholangiocarcinoma (pCCA), distal cholangiocarcinoma (dCCA), and intrahepatic cholangiocarcinoma (iCCA). The anatomical location of iCCA is within the biliary tree, whereas dCCA and pCCA, which are sometimes combined under the term extrahepatic cholangiocarcinoma (eCCA), originate outside the liver[1-3]. Between BTC subgroups and geographical areas, incidence and causes differ. In high-income nations, the incidence of CCA is modest (between 0.35 and 2 cases per 100000 people), but it can be up to 40 times higher in areas of Thailand and China where the disease is endemic. The incidence of iCCA is increasing in high-income countries. Statistics from the United Kingdom, the United States, and other countries show a consistent and steady growth in incidence from 0.1 to 0.6 instances per 100000 people during the last 30 years[4-6]. Hepatitis B and C infection, primary sclerosing cholangitis, liver fluke infections, liver cirrhosis, hepatolithiasis, Caroli's disease, obesity-associated liver disease, and diabetes are risk factors that have historically been associated to the development of BTC. It should be highlighted that the epidemiological disparities in the occurrence of different BTC types worldwide are also reflected in these risk variables[7-9]. The median overall survival (OS) for BTCs is 12 mo. Depending on stage, the 5-year relative survival rate for iCCA is from 9% to 25%, for eCCA it is between 10% and 15%, and for GBC it is between 15% and 35%[10,11]. The basic principle of curative therapy is radical surgery with negative margins; patients with early-stage illness, however, usually show no symptoms. Regrettably, the majority of BTC patients present with advanced BTC, with just a tiny fraction of BTCs being identified with a resectable condition[12,13]. The current gold standard for first-line treatment is still combined chemotherapy (CT) with gemcitabine and cisplatin (Gem/Cis) and second-line leucovorin (LV) calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX)[14,15]. However, there is no solid data concerning what to do next following the poor prognosis of chemotherapeutic treatment. The BTC landscape has recently witnessed the introduction of innovative medicines, including targeted medications like pemigatinib, infigratinib, and ivosidenib. Additionally, a number of cutting-edge therapies are being evaluated and have the potential to alter the therapeutic picture for these cancers, including immune checkpoint inhibitors (ICIs), either alone or in combination with other anticancer medicines[16-19]. In this review, we summarized recent clinical data on CT, targeted treatments, ICIs, and immunotherapy in the context of systemic treatment for BTCs.

CHEMOTHERAPY

First-line CT

Based on the outcomes of the Japanese BT22 Phase 2 and the Advanced Biliary Tract Cancer (ABC-02) Phase 3 studies, which showed that this combination was superior to gemcitabine alone, Gem/Cis is presently the recommended first-line treatment for patients with advanced BTC (aBTC)[14,20]. The results of this ground-breaking trial reported by Valle *et al*[21] showed that the combination of cisplatin and gemcitabine was associated with a longer median OS [11.7 mo *vs* 8.1 mo, HR: 0.64, 95% confidence interval (CI): 0.52-0.80; $P < 0.001$] and median progression-free survival (PFS) (8.0 mo *vs* 5.0 mo) compared with gemcitabine alone. Similar advantages of cisplatin-gemcitabine *vs.* gemcitabine monotherapy were also shown in the phase 2 BT22 study for Asian patients[22]. The efficacy of many combination CT treatments has been studied over the past ten years, including the triplet-agent

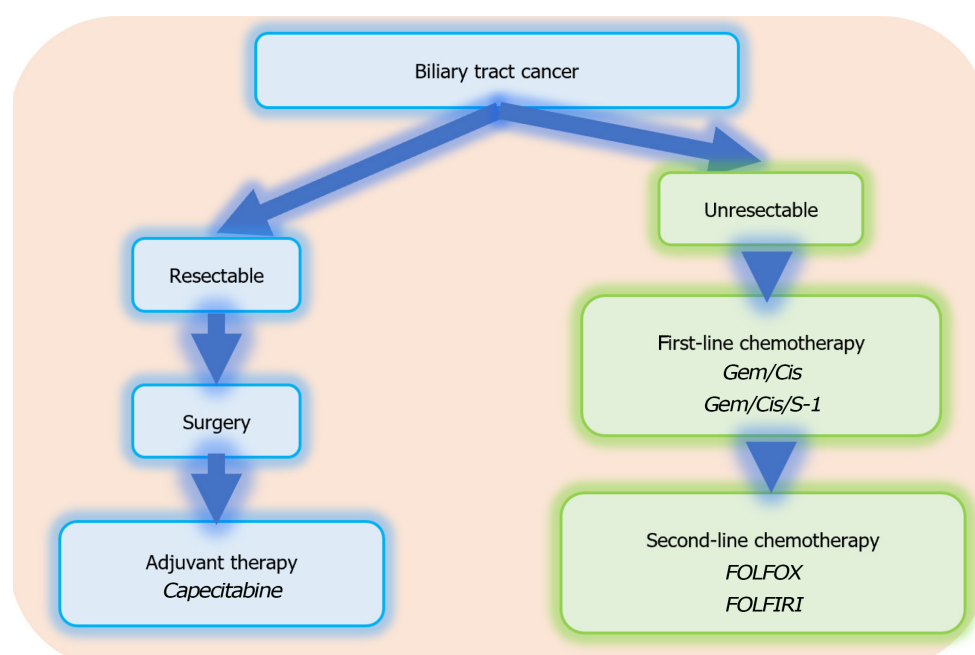
regimen, which combines Gem, Cis, and nab-paclitaxel (nab-P), and which has shown positive clinical results. Particularly, OS and PFS had medians of 19.2 and 11.8 mo, respectively[23,24]. In the real-world situation, Cheon *et al*[25] conducted a retrospective analysis in 178 Asian patients with advanced BTC to evaluate the treatment outcomes of Gem/Cis/nab-P. Gem/Cis/nab-P was administered as the initial course of treatment to 117 (65.7%) patients, whereas gemcitabine-based CT with nab-P was administered to 61 (34.3%) patients. The total objective response rate (ORR) for all patients was 42.1%, with a disease control rate (DCR) of 84.8%. In Korean patients with advanced BTC, they discovered that Gem/Cis/nab-P had positive real-life effectiveness and safety results that were consistent with the findings of the phase II study. However, Jung *et al*[26] evaluated the efficacy of triplet and normal doublet CT in a real-world scenario of 68 BTC patients and discovered that Gem/Cis/nab-P treatment did not increase PFS or OS compared to regular CT in patients with advanced BTC. They recommended that sizable randomized controlled studies are necessary to examine the advantages of triplet CT in advanced BTC.

A French team recently compared 5-fluorouracil (5-FU), oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) with the standard of care (SOC). One hundred and ninety-one patients with locally advanced or metastatic BTCs were randomized to receive either Gem/Cis for a maximum of 6 mo or infusional 5-FU without bolus, oxaliplatin, and irinotecan [modified FOLFIRINOX (mFOLFIRINOX)]. The study's primary OS endpoint was not met; the SOC in the first-line scenario was maintained with a median OS of 11.7 mo for mFOLFIRINOX and 13.8 mo for the Gem/Cis arm[27]. The development of S-1 in conjunction with platinum is ongoing in this line for BTC. In a phase 3 randomized controlled trial, the FUGA-BT study comprised 354 CT-unexperienced patients with recurrent or unresectable BTC with an ECOG of 0 or 1. OS is the primary endpoint of the non-inferiority study FUGA-BT, which compares Gem/S-1 to Gem/Cis. In Japanese patients, CT based on Gem/S-1 was not inferior to Gem/Cis. Patients allocated to the Gem/Cis group had a median OS of 13.4 mo, whereas those assigned to the S1-gemcitabine group had a median OS of 15.1 mo. Overall, there was good tolerability of the side effects, which did not substantially differ across treatment arms[28]. Recently, Ioka *et al*[29] conducted a multicenter, randomized phase 3 trial in 246 patients from 39 medical centers in Japan. Patients who had been enrolled were randomly assigned (1:1) to the Gem/Cis/S-1 (GCS) or Gem/Cis arm. The GCS regimen included 80 mg/m² of S-1 on days 1 through 7 every 2 wk, as well as infusions of cisplatin (25 mg/m²) and gemcitabine (1000 mg/m²) on day 1. OS was the main outcome, whereas PFS, ORR, and adverse events (AEs) were the secondary endpoints. They discovered that the median OS and 1-year OS rates in the GCS arm were 13.5 mo and 59.4%, respectively, whereas in the GC arm they were 12.6 mo and 53.7%. In the GCS arm, the median PFS was 7.4 mo, whereas in the GC arm, it was 5.5 mo. RR in the GCS arm was 41.5%, compared to 15.0% in the GC arm. AEs with a grade of 3 or below did not reveal any appreciable variations between the two arms. They stated that GCS may become the new first-line SOC for advanced BTC because it was the first regimen to show survival advantages as well as a higher RR than GC in a randomized phase 3 study (Figure 1).

Second-line CT

Combination regimens utilizing fluoropyrimidines, platinum salts, and other chemotherapies have been evaluated for the second-line situation. Results from a second-line randomized phase 3 trial were recently published. A United Kingdom population with locally advanced or metastatic BTC after progressing to first-line Gem/Cis CT with an ECOG 0-1 was involved in the open-label, phase 3 ABC-06 clinical research. The treatment of active symptom management plus FOLFOX or active symptom control alone was randomly allocated to 162 patients. Oxaliplatin (85 mg/m²) was administered as a 2-h infusion on day 1 of the FOLFOX CT regimen, followed by a 2-h infusion of LV (175 mg/m²/day), a 5-FU bolus (400 mg/m²/day), and a 46-h infusion of 5-FU (2400 mg/m²) every two weeks. OS among the population who were being treated intentionally was the main result. With 6.2 mo as opposed to 5.3 mo in the control group, FOLFOX slightly increased the median OS. Compared to 39% of patients in the control arm, 59% of patients in the experimental arm had grade 3/4 toxicities, such as fatigue and neutropenia. All subtypes of BTC tumors improved equally after FOLFOX in the subgroup study[30]. Patients who received FOLFOX as second-line treatment had a clinically significant increase in OS rates at 6 and 12 mo, despite the small absolute median OS difference between the two groups, and the study has produced clinical data for the first time in this context (Figure 1). For advanced BTCs, more cutting-edge CT regimens are being investigated in the second-line setting. A phase 2 study assigned 120 patients to either modified fluorouracil, and oxaliplatin (mFOLFOX) (5-FU 2400 mg/m² over 46 h, LV 100 mg/m² over 2 h, and oxaliplatin 100 mg/m² over 2 h, every 2 wk) or mFOLFIRI (5-FU 2400 mg/m² over 46 h, LV 100 mg/m² over 2 h, and irinotecan 150 mg/m² over 2 h, every 2 wk). The mFOLFOX group had a higher median OS (6.6 mo), ORR (5.9%), and median PFS (2.8 mo)[31].

A novel regimen, platinum-free liposomal irinotecan in combination with 5-FU/LV, has recently been studied in second-line BTC. In a randomized, open-label, phase IIb study, 174 Korean patients were randomly allocated to receive 5-FU/LV every two weeks or nal-IRI 70 mg/m² combined with 2400 mg/m² intravenous fluorouracil and intravenous LV 400 mg/m² for 46 h (NIFTY study). When compared to 5 FU/LV, the nal-IRI with 5-FU/LV improved PFS and OS significantly. In comparison to the 5-FU/LV group, which had a median PFS of 5.5 mo *vs* 1.4 mo, the nal-IRI plus 5-FU/LV group had a median PFS of 3.9 mo and a median OS of 8.6 mo. Even though this clinical trial is in phase 2b, there are



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Figure 1 Treatment strategy in biliary tract cancers. FOLFIRI: 5-fluorouracil plus irinotecan; FOLFOX: 5-fluorouracil plus oxaliplatin; Gem/Cis: Gemcitabine plus cisplatin; Gem/Cis/S-1: Gemcitabine plus cisplatin plus S-1.

exactly the same number of participants as in the single-phase 3 study that has been conducted to date (ABC-06). In the nal-IRI plus 5-FU/LV group, 70% of patients and 31% of patients in the 5-FU/LV group experienced grade 3 side effects, such as neutropenia and asthenia. Despite the fact that these outcomes are encouraging, they must be validated in global phase 3 clinical studies[32]. In a phase 2 trial in 2018, irinotecan 180 mg/m² on day 1 combined with capecitabine 1000 mg/m² twice daily on days 1 through 10 (XELIRI-arm) or irinotecan 180 mg/m² on day 1 alone (IRI-arm) were the two therapy options given to 60 Gem/Cis refractory aBTC patients by Zheng *et al*[33] over the course of a cycle of 14 d. Treatments were continued until the condition became worse or the side effects became too severe. They discovered that the median PFS was 3.7 *vs* 2.4 mo, the 9-mo survival rate was 60.9% *vs* 32.0%, the median OS was 10.1 *vs* 7.3 mo, and the DCR was 63.3% *vs* 50.0% for the XELIRI-arm and IRI-arm, respectively. Leucopenia and neutropenia were the two grade 3 or 4 toxicities that were most prevalent.

Because of a number of factors, including the proportion of patients deemed suitable for third- or later-line treatment and the absence of agreement for second-line therapy prior to ABC-06 and NIFTY, few studies have looked at the usefulness of systemic CT in the third-line situation. There are few data on third-line CT for highly pretreated patients. As a result, the clinical choice of third-line CT in metastatic BTC remains complex and is based on a number of factors, including the patient's motivation, performance status, response to prior therapies, and quality of life[34,35].

TARGETED THERAPIES

More driving genes are being discovered because of the advancement of next-generation sequencing, which is assisting in the creation of new treatments as well as the explanation of the pathophysiology of BTC. In the BTC landscape, iCCA, eCCA, GBC, and AVC appear to differ significantly from one another based on this technology. Kirsten rat sarcoma virus (RAS), AT-rich interactive domain B mutations, and erb-b2 receptor tyrosine kinase 2 (ERBB2) are more common in eCCA and GBC, whereas isocitrate dehydrogenase (IDH)-1, IDH-2 mutations, and FGFR2 fusions or rearrangements are almost exclusively detected in intrahepatic variants[36,37].

FGFR2 inhibitors

According to several genetic studies, FGFR2 abnormalities are seen in about 15%–25% of iCCAs. Tyrosine kinase receptors known as FGFRs are implicated in regulating RAS, Janus kinase 2, and phosphoinositide 3-kinases (PI3K)/mammalian target of rapamycin pathways, and FGFR2 abnormalities affect cellular migration, angiogenesis, proliferation, and survival processes[38,39]. Numerous medications that target FGFR isoforms, including infigratinib, pemigatinib, derazantinib, erdafitinib (ATP-competitive, reversible inhibitors), and futibatinib (non-ATP-competitive, covalent

inhibitor), have been studied in iCCA patients during the past ten years[40,41]. In a phase 1 clinical trial with 3 CCA patients carrying FGFR2 abnormalities, the pan-FGFR tyrosine kinase inhibitor infigratinib was originally evaluated, and all patients had stable condition[42]. In a further phase 2 study, infigratinib was investigated in 61 gemcitabine-resistant CCA patients with FGFR2 gene mutations, fusions, or amplifications. In the subset of CCAs with FGFR2 gene fusions, the ORR and DCR, respectively, were 19% and 83%; the most frequently reported side effects were tiredness, hyperphosphatemia, baldness, and stomatitis[43]. Javle *et al*[44] recently published the complete data of this single-arm, phase 2 study, in which infigratinib showed a median PFS and OS of 7.3 mo and 12.2 mo, respectively (Table 1).

In a multicenter, open-label, single-arm phase 2 trial (FIGHT-202) with three cohorts: 107 patients with FGFR2 fusions or rearrangements, 20 patients with other FGFR alterations, or 18 patients without such changes, pemigatinib, another reversible inhibitor, was investigated. The main outcome measure was ORR in patients with FGFR2 fusions or rearrangements who took pemigatinib at least once. With three cases of full response and a median treatment time of 7.2 mo, ORR was observed in 35.5% (38/107) of patients with FGFR2 gene fusions and/or rearrangements during the course of their median follow-up of 17.8 mo. The median PFS and OS for this cohort were 6.9 and 21.1 mo, respectively. The other two cohorts of CCA patients, however, did not have any responses; in patients with additional FGF/FGFR mutations, the median PFS was 2.1 mo and the median OS was 4.0 mo, whereas the median PFS in patients with FGFR wild type was 1.7 mo. Patients with FGFR2 gene fusions and/or rearrangements had a median OS of 17.5 mo (95% CI: 14.4-22.9)[45]. Pemigatinib was given fast approval by the United States Food and Drug Administration for pretreated patients with metastatic CCA that included FGFR2 fusions or rearrangements as a consequence of the findings of FIGHT-202. Following these encouraging findings, in patients with FGFR2 rearrangements as the first-line scenario, the phase 3 FIGHT-302 and PROOF-301 investigations, in which both therapies are contrasted with Gem/Cis, are evaluating FGFR2 inhibitors[46,47].

In a phase 1/2 study (AR087-101) involving 29 CCA patients with FGFR2 gene fusion, the pan-FGFR inhibitor derazantinib (ARQ087) was first analyzed. Two cases of therapy-naïve CCA were included, although the bulk of the patients ($n = 27$) had had disease progression after at least one systemic treatment. According to the study's findings, with a median PFS of 5.7 mo, the ORR and DCR were 20.7% and 82.8%, respectively[48]. Erdafitinib (JNJ-42756493), a different pan-FGFR inhibitor, was studied in a phase 1 study and shown to be effective in CCA patients with FGFR mutations or gene fusions, with an ORR of 27.3% and an average response time of 11.4 mo[49]. Futibatinib (TAS-120), an irreversible, highly selective pan-FGFR inhibitor that can overcome resistance to ATP-competitive inhibitors, is the final potential drug. All iCCA patients ($n = 3$) exhibited a partial response in the first dose-escalation phase 1 study that included metastatic solid tumors with FGFR abnormalities[50]. Following the findings of this trial, 67 pretreatment iCCA patients with FGFR2 gene fusions or rearrangements were included in the FOENIX-CCA2 single-arm, multicenter, phase 2 trial. The findings of this trial showed that an ORR was noted in 42.0% of patients receiving futibatinib, with a median PFS of 9.0 mo and a median OS of 21.7 mo[51]. Futibatinib was associated with a number of the same treatment-related side effects as other FGFR inhibitors, such as diarrhea, hyperphosphatemia, alopecia, and dry mouth. The phase 3 FOENIX-CCA3 clinical research is evaluating futibatinib *vs* Gem/Cis as a first-line treatment for locally progressed, unresectable, or metastatic iCCA patients with FGFR2 gene fusions or rearrangements in light of the encouraging signs of efficacy reported in FOENIX-CCA2 (Figure 2).

IDH inhibitors

IDH mutations are very uncommon findings in the other BTC subtypes, such as eCCA and GBC; however, they have been documented in about 15% of all cases with iCCA. From a biological perspective, IDH mutations inhibit enhanced IDH1/2 activity, resulting in modifications to cellular metabolism and a buildup of the tumor metabolite 2-hydroxyglutaric acid (2-HG). IDH1/2 mutations in the isocitrate binding region reduce enzyme activity for oxidative decarboxylation of isocitrate to α -ketoglutarate. In turn, 2-HG alters DNA methylation and chromatin structure in a number of ways that hinder normal cell differentiation and promote cancer. This genetic change allows tumors to catalyze the conversion of α -ketoglutarate to 2-HG. This has recently been studied in patients with CCA, and several of these drugs have already demonstrated encouraging benefits in other malignancies with IDH mutations[52,53]. A number of IDH1/2 inhibitors, including ivosidenib, enasidenib, and others, have lately been investigated in CCA patients; some of these drugs have already shown notable benefit in other malignancies with IDH mutations.

An oral IDH1 targeted inhibitor called ivosidenib (AG-120) has demonstrated efficacy in preliminary clinical studies. The pivotal experiment that led to the approval of ivosidenib was the multicenter, randomized, double-blind, placebo-controlled ClarIDHy phase 3 study, patients with advanced, IDH1-mutant CCA who had progressed on up to two prior therapy regimens were enrolled. IDH1 mutations were prescreened in a total of 780 individuals, and 187 were randomly assigned to receive either 500 mg of ivosidenib once daily or a placebo. The majority of them were advanced iCCA at the time of randomization. In the ivosidenib group, the median PFS was 2.7 mo as opposed to 1.4 mo in the placebo group; this improvement was statistically significant. Ivosidenib's median OS was 10.3 mo while the placebo

Table 1 Summary of main clinical trials evaluating the targeted therapies in advanced biliary tract cancer patients

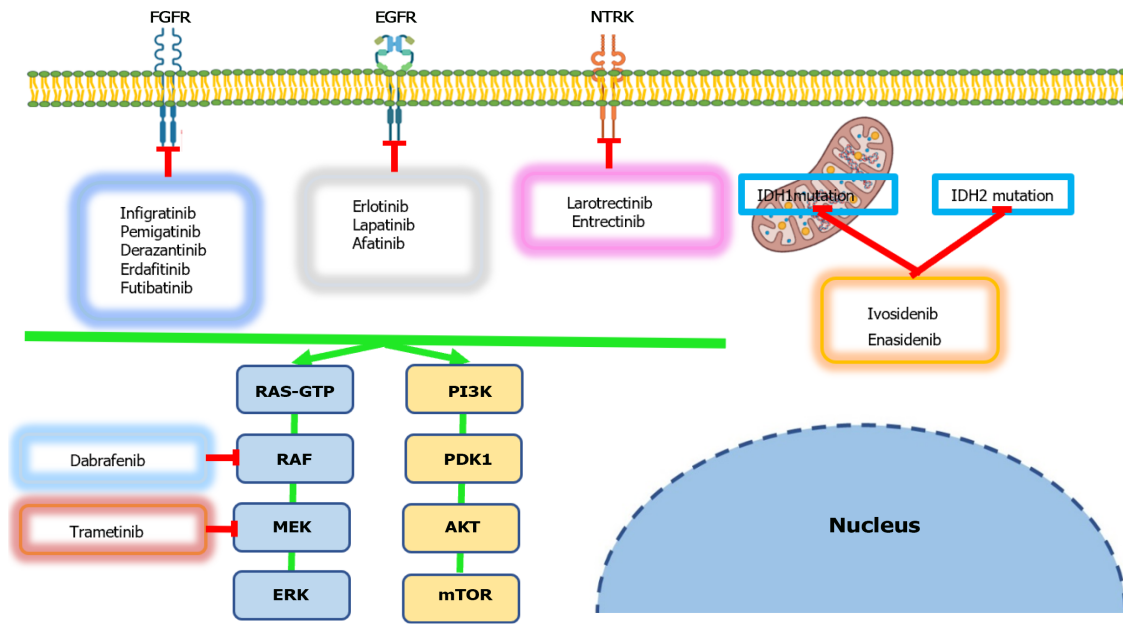
Ref.	Country	Drug(s)	Number of patients	Study phase	ORR (%)	Mean OS (months)	Mean PFS (months)	Adverse events
FGFR2 inhibitors								
Javle <i>et al</i> [44]	United States, Belgium, Spain, Germany, Singapore, Taiwan, and Thailand	Infigratinib (BGJ398)	108	2	23.1	12.2	7.3	Tiredness, baldness, hyperphosphatemia, and stomatitis
Abou-Alfa <i>et al</i> [45]	United States, France, Italy, Germany, Belgium, and South Korea	Pemigatinib (FIGHT-202)	146	2	35.5	21.1 (FGFR2 fusion)	6.9 (FGFR2 fusion)	Hypophosphatemia, arthralgia, stomatitis, hyponatremia, and abdominal pain
Mazzaferro <i>et al</i> [48]	United States and Italy	Derazantinib (AR087-101)	29	1/2	20.7	12.7	5.7	Fatigue, eye toxicity, hyperphosphatemia, and increase in ALT/AST
Bahleda <i>et al</i> [49]	United States, France, and Spain	Erdafitinib (JNJ-42756493)	11	1	27.0	12.0	7.5	Fatigue, eye toxicity, hyperphosphatemia, and increase in ALT/AST
Goyal <i>et al</i> [51]	United States, France, Spain, United Kingdom, Netherlands, Japan, Germany, and South Korea	Futibatinib (TAS-120)	103	2	42.0	21.7	9.0	Hyperphosphatemia, diarrhea, fatigue, alopecia, and stomatitis
IDH inhibitors								
Zhu <i>et al</i> [54]	United States, China, Spain, United Kingdom, Ireland, and South Korea	Ivosidenib (AG-120)	187	3	51.0	10.3	2.7	Ascites, anemia, increase bilirubin level, and hyponatremia
BRAF inhibitors								
Subbiah <i>et al</i> [59]	United States, Denmark, United Kingdom, Austria, France, Italy, Spain, Germany, Netherlands, Switzerland, Japan, and South Korea	Trametinib and Dabrafenib	43	2	47.0	14.0	9.0	Hypertension, reduced white blood cell count, and elevated gamma-glutamyl transferase
NTRK inhibitors								
Doebele <i>et al</i> [67]	United States, France, Italy, Spain, Germany, Australia, Hong Kong, Switzerland, Japan, and South Korea	Entrectinib	54	1/2	57.0	21.0	11.0	Anemia, increased weight, dyspnea, and fatigue

BRAF: B-Raf gene; FGFR2: Fibroblast growth factor receptor 2; IDH: Isocitrate dehydrogenase; NTRK: Neurotrophic tyrosine receptor kinase; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

group's median OS was 7.5 mo. The 57% crossover from placebo to ivosidenib, which was authorized on the basis of radiological advancement, may be the cause of the OS difference that was not statistically significant. Nausea, diarrhea, and exhaustion were common side effects that affected 41%, 35%, and 31% of individuals, respectively[54]. Rimini *et al*[55] presented the first real-world experience in 2022, with eight patients with previously treated locally advanced or metastatic IDH1-mutated CCA treated with ivosidenib after a median follow-up of 9.4 mo. They discovered that the median OS was not attained, while the median PFS from the commencement of therapy with ivosidenib was 4.4 mo. The DCR was 62.5%, with two patients attaining a partial response (at a rate of 25%). 12.5% of patients had side effects due to the therapy, however, none of grade 3 or higher were noted. Hypomagnesemia and a longer QT interval were the grade 2 AEs that were detected. They concluded that the effectiveness results were in line with those mentioned in the ClarIDHy study. Larger samples of real-world data are required to corroborate the findings[56]. Other IDH inhibitors, like as enasidenib (AG-221), and combination therapy combining these targeted drugs with additional anticancer drugs, such PARP inhibitors, are now being evaluated in IDH-mutated CCAs.

BRAF inhibitors

BRAF is a growth signal transduction protein kinase that belongs to the Raf kinase family. The mitogen-activated protein (MAP) kinase/extracellular signal-regulated kinases signaling system, which controls



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Figure 2 Targeted therapies used in systemic treatment for biliary tract cancers. AKT: Protein kinase B; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-related kinase; FGFR: Fibroblast growth factor receptor; GTP: Guanosine triphosphate; IDH1: Isocitrate dehydrogenase 1; IDH2: Isocitrate dehydrogenase 2; MEK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; NTRK: Neurotrophic tyrosine receptor kinase; PI3K: Phosphoinositide-3-kinase; PKD1: Polycystic kidney disease 1; RAF: Raf proto-oncogene; RAS: RAS proto-oncogene.

cell division, differentiation, and secretion, is regulated by this protein. Approximately 5% of BTCs have been shown to contain BRAF gene alterations, particularly in iCCA. Fascinatingly, individuals with BRAFV600E mutations experience more aggressive clinical behavior, have more advanced tumors upon diagnosis, and are more likely to have lymph node involvement. Similar to other BRAF-mutated cancers, this situation has exhibited the early emergence of treatment resistance and transient responses to BRAF inhibitor monotherapy[57,58]. Consequently, combination therapies combining BRAF inhibitors and MEK inhibitors have been investigated. Subbiah *et al*[59] conducted a phase 2, open-label, single-arm study, the Rare Oncology Agnostic Research, to assess the effectiveness and safety of trametinib and dabrafenib in 43 patients, including 91% with iCCA, 2% with pCCA, 2% with GBC, and 2% with unclear origins. Independent analysis revealed a 47% ORR, a 9-mo median PFS, and a 14-mo median OS. These results demonstrated that, in contrast to metastatic colorectal cancer, where EGFR inhibition is crucial, BRAF inhibition is critical in BTC. Among patients taking dabrafenib with trametinib, hypertension (7%), a decrease in white blood cell count (7%), and an increase in gamma-glutamyl transferase (12%) were the most common grade 3 or 4 AEs. The dual-targeting treatment appears to produce better results than BRAF inhibition alone. Future research should concentrate on the use of combination drugs for early therapy.

EGFR inhibitors

Human EGFR2 (HER2) is a tumor-promoting growth factor receptor. EGFR, HER1 (ERBB1), HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4) are all members of the same family. These transmembrane growth factor receptors activate downstream secondary messengers when their intracellular domains are phosphorylated, resulting in a variety of physiologic consequences. HER2 activation causes cancer by activating the MAP kinase and PI3K pathways, as well as a loss of cell polarity and adhesion and a disrupted cell cycle by activating cyclin D and inhibiting p27. The most active catalytic kinase is seen in HER2, especially when HER3 is involved. The HER2 protein has been shown to be overexpressed in 13% of GBCs and up to 18% of eCCA[60,61]. Although HER2 overexpression has been correlated with a poorer prognosis and a higher tendency to metastasize, it has also been associated with increased cytotoxic and targeted agent sensitivity. Javle *et al*[62] retrospectively analyzed patients with advanced GBC and CCA who had HER2/neu-directed therapy between 2007 and 2014 and who had HER2/neu genetic abnormalities or protein overexpression. HER2/neu-directed treatment (trastuzumab, lapatinib, or pertuzumab) had been administered to five patients with CCA and nine patients with GBC at some point throughout the research. Eight incidences of HER2/neu gene amplification or overexpression in GBC patients were found. With HER2/neu-directed treatment, these patients either had a full response ($n = 1$), a partial response ($n = 4$), or disease stability ($n = 3$). A HER2/neu mutation caused a patient who received lapatinib therapy to have a mixed response. Response times ranged from 8 to 168 wk (median 40 wk). The CCA cases in this series that were treated had a greater proportion of HER2/neu mutations,

and despite HER2/neu-directed treatment, these patients showed no radiological responses. They recommended that HER2/neu blocking is a promising therapeutic approach for patients with gene amplification for GBC and merits more investigation in multicenter research.

Neurotrophic tyrosine receptor kinase inhibitors

Three membrane-bound receptors known as tropomyosin receptor kinases (Trk A, B, and C) are encoded by the neurotrophic tyrosine receptor kinase genes (NTRK1-3), which are exceedingly uncommon in BTC (0.67%) and present in between 0.3% and 1% of all solid tumors. The cytoplasmic kinase is activated by neurotrophin binding, which also activates the MAPK, PI3K, and phospholipase C- γ 1 pathways and downstream signaling cascades. One of the three *NTRK* genes can combine with a number of partners to form oncogenic fusions, which constitutively activate the Trk pathway and promote cancer[63-65]. Larotrectinib and entrectinib, two extremely specific small compounds that inhibit all three TRK proteins, were discovered and demonstrated efficacy in preliminary clinical studies. Larotrectinib (LOXO-101) phase 1 clinical trial, which recruited 55 patients, was analyzed, and it was revealed that the ORR was 75% and the median PFS was not attained until 9.9 mo. There were only 2 CCA patients included, and both had an ORR of 80%. One patient had a progressing condition[66]. Three entrectinib phase 1 or 2 clinical studies (STARTRK-1, STARTRK-2, and ALKA-372-001) were analyzed together. Fifty-four patients from 10 distinct NTRK fusion-positive tumor types were enrolled in all of the studies, which showed a median PFS of 12.9 mo and an ORR of 57%[67].

ICIS

The incorrect insertions or deletions that happen during DNA replication are recognized and corrected by the mismatch repair (MMR) mechanism. ICIs are particularly effective against cancers with a deficient MMR (dMMR) system because these cancers frequently have somatic mutations. Adenocarcinomas of the liver, cervix, endometrium, and gastrointestinal tract all have dMMR in more than 5% of cases. They are observed in localized phases more frequently (8%) than in metastatic stages (4%). Depending on the region and published series, dMMR accounts for 2%–18% of tumors in BTC. In contrast to eCCA or GBC (5%–8%), it is more common in iCCA (10%) and AVC (6%–20%)[68,69]. ICIs can boost anticancer activity by inhibiting immune system regulators like cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and lymphocyte activating gene 3. This results in increased cytotoxicity in T lymphocytes (Figure 3). ICIs have recently been tested in BTC, either by alone or in combination with other anticancer drugs[70-73].

Both the phase 1b and phase 2 KEYNOTE-158 studies used the PD-1 inhibitor pembrolizumab. In these two studies, a limited group of BTC patients who had already had treatment and whose conditions had gotten worse on traditional therapy were involved. The median PFS and OS for KEYNOTE-158 were 2.0 and 7.4 mo, respectively, whereas the ORR, median PFS, and median OS for KEYNOTE-028 were 13.0%, 1.8 mo, and 5.7 mo, respectively, in the intention-to-treat group. Microsatellite instability (MSI) status was used by the investigators to stratify their data, and patients with MSI-H/dMMR had an ORR of 40.9% with median PFS and OS of 4.2 and 24.3 mo, respectively [74]. Metastatic BTC was treated with nivolumab, a human immunoglobulin G4 monoclonal antibody that prevents PD-1 interaction with PD-L1 and PD-L2. Early results from a single-group, multicenter phase 2 study of nivolumab monotherapy showed partial responses in 10 of 45 patients with CCA who had previously received treatment, with 27 of them reaching a stable status. It is also worth noting that the median PFS and OS were 3.68 and 14.24 mo, respectively. Nivolumab was further assessed as a first-line treatment for patients with metastatic condition when combined with the traditional doublet Gem/Cis, with results indicating a median OS of 15.4 mo and a median PFS of 4.2 mo. Moreover, 11 out of 30 patients showed an objective response[75].

Ueno *et al*[76] performed a multicenter, open-label, phase 1 trial in 60 patients with BTCs to investigate the safety and tolerability of the ICI nivolumab as monotherapy or in combination with Gem/Cis CT. Nivolumab monotherapy (240 mg every 2 wk) was given to 30 patients with unresectable or recurrent BTC that was resistant or intolerant to Gem/Cis. Thirty CT-naïve patients with unresectable or recurrent BTC were given nivolumab (240 mg every two weeks) in addition to Gem/Cis CT. In the monotherapy cohort, they found that the median OS was 5.2 mo, the median PFS was 1.4 mo, and just one patient out of thirty exhibited an objective response. Eleven out of 30 patients in the combination treatment cohort showed an objective response, and the median OS and PFS were 15.4 and 4.2 mo, respectively. They concluded that nivolumab showed evidence of therapeutic effectiveness in individuals with unresectable or recurrent BTC and had a tolerable safety profile. This preliminary evaluation of nivolumab for the treatment of advanced BTC offers encouraging data for upcoming larger randomized studies of nivolumab in this challenging malignancy.

Nivolumab was also investigated in a phase 2 trial on 54 patients with refractory BTC at doses of 240 mg intravenously every two weeks for 16 wk, followed by 480 mg intravenously every four weeks, until disease progression or unacceptable toxicity. According to the research, the ORR by central review was

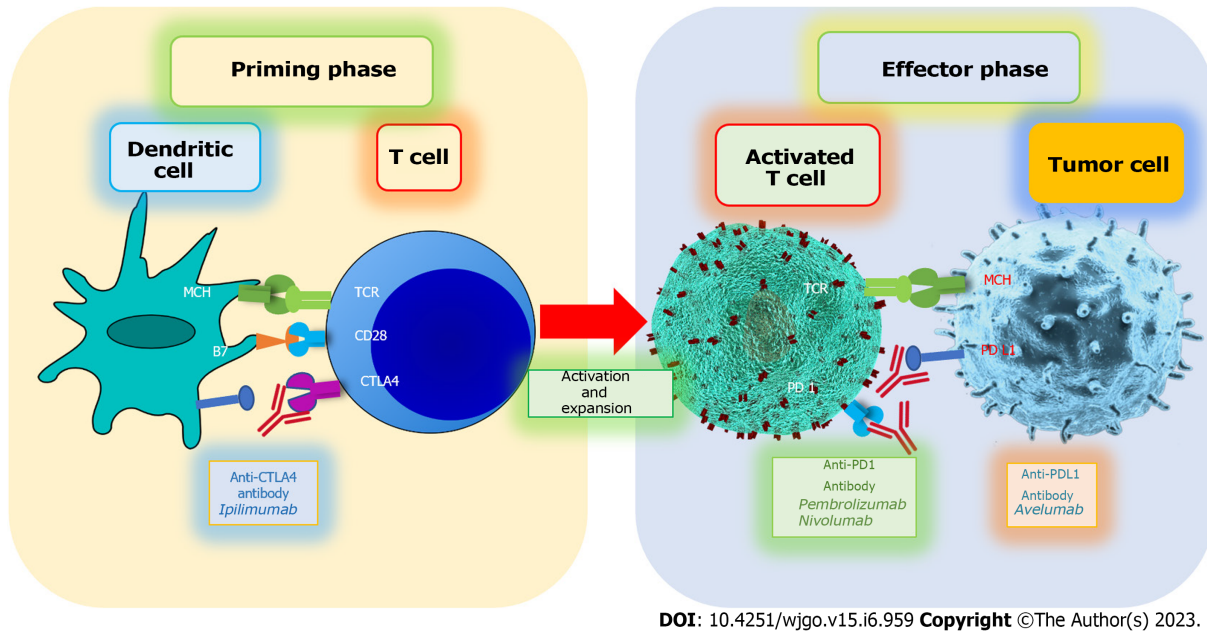


Figure 3 The mechanisms of action of immune checkpoint inhibitors in cancer immunotherapy. CTLA-4: Cytotoxic T lymphocyte antigen 4; MHC: Major histocompatibility complex; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; TCR: T cell receptor.

11%, the DCR was 50%, the median PFS was 3.7 mo, and the median OS was 14 mo. The median PFS and OS were higher for patients who were stratified by positive PD-L1 expression status than for patients who had PD-L1-negative expression[77]. Nivolumab and the anti-CTLA-4 drug ipilimumab were studied in combination in patients with advanced BTCs by Klein *et al*[78]. The median PFS was 2.9 mo, the ORR was 23%, 17 out of 39 patients had disease control, and the median OS was 5.7 mo. The ORR for patients with iCCA and GBC was 31%, while there was no response seen in individuals with eCCA, suggesting that the effectiveness of ICIs varied depending on the anatomic locations. In an advanced BTC patient without prior systemic treatment and an ECOG score of 0-1, Sahai *et al*[79] conducted a phase 2 randomized study to assess the impact of adding an anti-PD-1/PD-L1 antibody to either systemic CT or an anti-CTLA4 antibody. Nivolumab (360 mg) was given to patients in Arm A (35) on day one, along with Gem/Cis on days one and eight, every three weeks for six months, followed by Nivolumab (240 mg) every two weeks. Patients in Arm B (33) received nivolumab (240 mg) every two weeks, and Ipilimumab (1 mg/kg) every six weeks. They discovered that the 6-mo PFS rates in Arm A were 59.4% and Arm B was 21.2% for the observed main endpoint. The median PFS and OS in Arm A were 6.6 and 10.6 mo, respectively, while they were 3.9 and 8.2 mo in Arm B. The most common grade 3 or higher hematologic AE related to therapy was neutropenia (34.3%, Arm A), while tiredness (8.6%, Arm A) and elevated transaminases (9.1%, Arm B) were the most common nonhematologic AEs. They determined that when combined with CT or Ipilimumab, Nivolumab did not improve 6-mo PFS. Although both arms' median OS was less than 12 mo, Arm A's high OS rate at 2 years suggested benefit in a small patient cohort.

A phase 2 trial with advanced BTC examined gemcitabine and oxaliplatin (GEMOX) and the PD-1 antibody, camrelizumab. Fever and exhaustion were the side effects of therapy that occurred most frequently (both 73%). In 54% of patients, the combination produced an objective response. When compared to those for GEMOX alone, the median PFS was 6.1 mo and the median OS 11.8 mo[80]. Patients with advanced BTC were evaluated in a phase 2 research study in China using camrelizumab plus an oxaliplatin-based CT regimen. Similar to the ABC-02 study, the reported ORR was 16.3%, the median PFS was 5.3 mo, and the median OS was 12.4 mo. These encouraging findings imply that a novel first-line treatment for advanced BTC, camrelizumab plus oxaliplatin-based CT, may be possible [81]. In a phase 2 study, individuals with advanced BTC who had never had CT were given a combination of Gem/Cis plus durvalumab, with or without tremelimumab. Three regimens of CT and immunotherapy were administered to all patients, and the medication dosages across the regimens were all the same. They enrolled 128 patients; 32 in the Gem/Cis, followed by the Gem/Cis plus durvalumab and tremelimumab, 49 in the Gem/Cis plus durvalumab, and 47 in the Gem/Cis plus durvalumab and tremelimumab. The total median PFS was 12.1 mo and the median OS was 18.4 mo, which was encouraging compared with traditional CT. The research, however, lacked a control group. There were no appreciable changes in OS or PFS across the three regimens. After one cycle of therapy, the researchers discovered that lower PD-L1 expression in immune and tumor cells was linked to a shorter PFS. Immune cell PD-L1 expression was connected to the median OS. The findings suggested that PD-L1 expression variations following therapy may help predict clinical outcomes. Considering the

promising potential of CT combined with durvalumab in advanced BTC[82].

Peng *et al*[83] conducted a meta-analysis to assess the predictive and clinicopathological significance of the systemic immune-inflammation index (SII) in BTC. A combined study revealed that those with high SII levels had worse OS than people with low SII levels. Moreover, a higher SII was linked to lymph node metastases, TNM stage, and vascular invasion. In contrast, no significant relationship was discovered between a high SII and sex or tumor differentiation. These data indicated that high SII levels were associated with poor survival outcomes in individuals with BTC, as well as certain more malignant aspects of BTC.

CONCLUSION

Since BTC is frequently discovered at advanced stages, the disease is usually incurable. The best currently available, possibly curative treatment for a primary tumor found in the early stages in a subset of people is surgery; however, the treatment of advanced cancer is still in its early phases. As a result of biology's present understanding, new tactics are becoming possible because BTCs have several chemical changes that may be altered. Since several genetic abnormalities may be discovered and will affect our patients' outcomes, it is strongly recommended that all BTC patients receive a thorough molecular test before beginning systemic medication. There are several clinical trials taking place right now that use various methods to examine the safety and effectiveness of many medications in first- and second-line settings. Following the encouraging findings of phase 3 ABC-02, which showed an improvement in median OS compared with gemcitabine alone, the first-line recommended therapy is still Gem/Cis. However, the TOPAZ-1 clinical study, which revealed an improvement in OS, PFS, and ORR with immunotherapy combined with CT, has set a new course for patients who do not carry driver mutations. When compared to active symptom management, FOLFOX has demonstrated a little but statistically significant improvement in median OS. For BTC patients with certain genetic problems, targeted drugs such FGFR2, IDH1, and BRAF inhibitors have already demonstrated good outcomes in clinical trials. Targeted medicines, CT combinations, and ICIs are other approaches under investigation that will have an influence on the treatment of BTC in the future.

FOOTNOTES

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