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REVIEW ARTICLE

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Advances in targeted therapy of cholangiocarcinoma

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ABSTRACT

Cholangiocarcinoma (CCA) is a malignant tumor originating in the bile duct and its branching epithelium. Due to its high heterogeneity, there are no specific clinical indications at the early stage, the diagnosis is often in advanced CCA. With surgical resection, the 5-year postoperative survival rate (long-term survival rate) is very poor. The regimen of gemcitabine combined with platinum has been used as the first-line chemotherapy for advanced patients. In recent years, targeted therapy for a variety of malignant tumors has made great progress, showing good efficacy and safety in advanced CCA. However, the current targeted therapy of CCA still has many challenges, such as adverse reactions, drug resistance, and individual differences. Therefore, the researches need to further explore the targeted therapy mechanism of CCA malignancies in depth, develop more effective and safe drugs, and accurately formulate plans based on patient characteristics to further improve patient prognosis in the future. This article reviews the recent progress of targeted therapy for CCA, aiming to provide a strategy for the research and clinical work of targeted therapy for CCA.

KEY MESSAGES

- For these patients without surgical indications, chemotherapy and radiation therapy are the main treatment options, among which gemcitabine combined with cisplatin is the standard recognized chemotherapy regimen.
- With the gradual maturity of gene detection technology, the molecular pathology of CCA has gradually been revealed and precision oncology has become a promising method for the treatment of CCA.

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Introduction

Cholangiocarcinoma (CCA) is a highly fatal malignant tumor of the epithelial cells of the bile duct that occurs in the biliary tree and the liver parenchyma [1]. According to its anatomical subtypes, CCA can be divided into intrahepatic cholangiocarcinoma (ICC), perihilar cholangiocarcinoma (pCCA), and distal cholangiocarcinoma(dCCA) [2,3]. Due to anatomical differences in cholecystic duct insertion, pCCA and dCCA can collectively be termed extrahepatic cholangiocarcinoma (eCCA) [4,5]. The incidence of CCA is increasing and the epidemiology is different widely in the worldwide [6]. Its causes are complex, including living habits (smoking, drinking), infectious diseases (hepatitis, liver fluke), metabolic disease (diabetes, obesity, metabolic syndrome), liver/primary biliary disease (primary sclerosing cholangitis, bile duct cyst, bile duct, liver cirrhosis, inflammatory bowel disease, Caroli's disease) and toxic exposure (asbestos, thorium contrast agents, organochlorine solvent), etc [7]. In Southeast Asia, fluke hepatica is the main cause of ICC [8].

In fact, CCA has no obvious clinical manifestations in the early stage, and patients often present with jaundice, ascites, hepatomegaly, and other specific symptoms. Most patients are diagnosed as locally advanced, unresectable, or metastatic disease [9,10]. For these patients without surgical indications, chemotherapy and radiotherapy are the main treatment options, among which gemcitabine combined with

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cisplatin is the standard recognized chemotherapy regimen [11–13]. The 5-year survival rate of advanced disease is close to 5%, the median survival time is less than 1 year, and the prognosis of patients is extremely poor [14,15]. There is no established standard treatment for failure of first-line chemotherapy, second-line chemotherapy has limited efficacy in patients with advanced CCA, and data from the ABC-06 trial support the use of 5-fluorouracil and oxaliplatin (FOLFOX) in patients treated with cisplatin and gemcitabine [14]. A total of 162 patients enrolled in ABC-06 showed significant improvements in median overall survival and 1-year survival (5.3 months vs. 6.2 months; 11.4% vs. 25.9%), and grade 3–5 adverse events increased (52% vs. 69%)[16]. Radiotherapy such as stereospecific radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), brachytherapy such as selective internal radiotherapy (SIRT), and proton therapy have certain therapeutic effects on CCA. However, large adverse reactions and limited clinical data, etc., the therapeutic benefits of radiotherapy for the treatment of advanced CCA remain controversial [17,18]. In summary, chemotherapy mainly inhibits the growth of tumor cells through drugs to achieve the therapeutic purpose, it also has the power to kill normal cells at the same time. Radiotherapy can achieve radical effect on sensitive lesions and is relatively less traumatic, but the types of sensitive tumors are limited, and the requirements for equipment are high, so the general applicability is insufficient [19]. Therefore, it is clinically important to actively explore novel treatment modalities for CCA and to designate efficient treatment protocols.

In recent years, with the gradual maturity of gene detection technology, the molecular pathology of CCA has gradually been revealed and precision oncology has become a promising method for the treatment of CCA (Figure 1). The goal of precision oncology is to screen out potential populations that are more likely to benefit from treatment and provide patients with more targeted therapy strategies [20]. In recent years, the therapeutic efficacy of tumors has been significantly improved by the development of molecularly targeted drugs [21]. Many studies have shown that precision treatment has improved the survival rate and improved the prognosis of patients with breast cancer, lung cancer and other tumors [22–24]. However, only a few patients still obtain a lasting survival benefit, and most patients quickly develop drug resistance during treatment in clinical practice. Up to 70% of ICC may have at least one targeted gene mutation [25,26]. Common therapeutic targets include the fibroblast growth factor receptor 2 (FGFR2, 14%), KRAS(11%), phosphatase and tensin homolog deleted on chromosome ten (PTEN, 11%), cyclin-dependent kinase

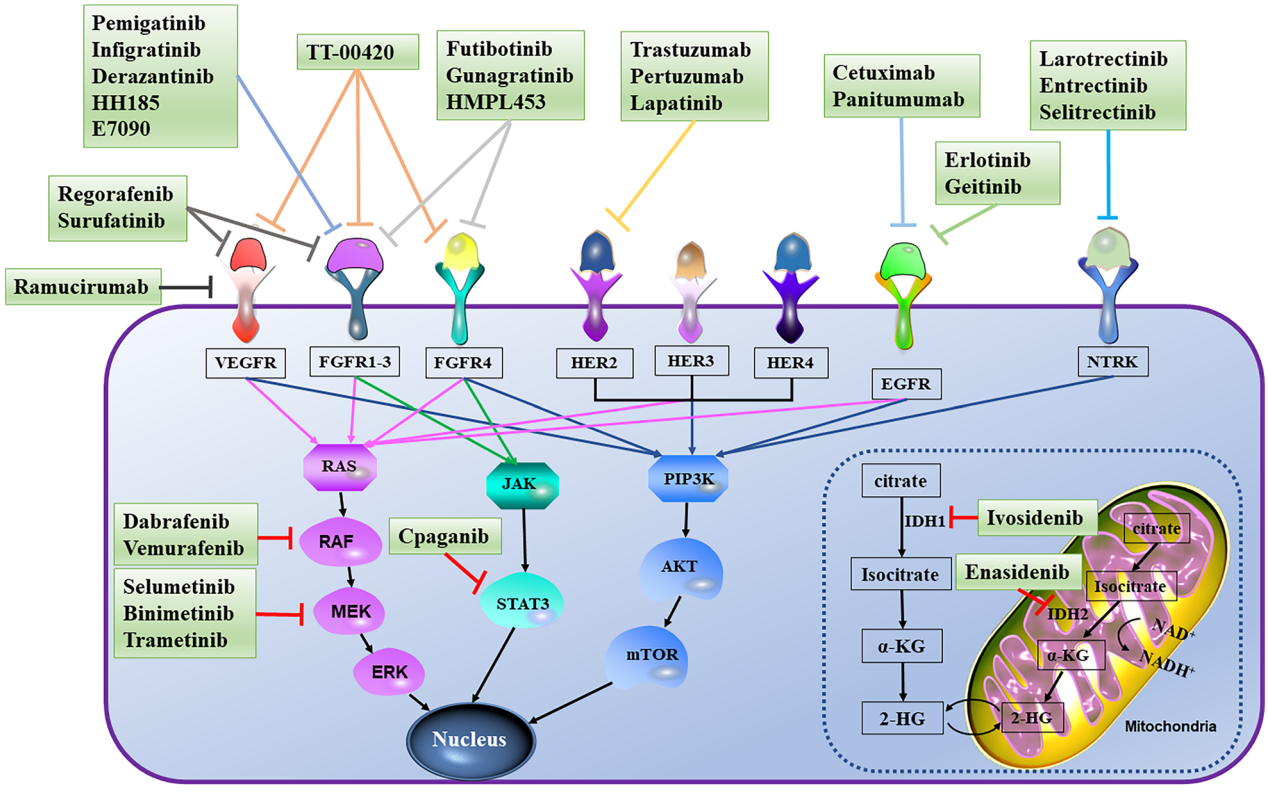


Figure 1. Targets and mechanisms of different drugs in cholangiocarcinoma.

inhibitor 2 A/B (CDKN2B, 7%), ERB-B2 receptor tyrosine kinase 3 (ERBB3, 7%), MET (7%), NRAS (7%) and CDK6 (7%), BRCA1 (4%), BRCA2 (4%), the NF1 (4%), PIK3CA (4%), PTCH1 (4%) and the TSC1 gene (4%) [25]. To mark these targets, common targeted drugs include fibroblast growth factor receptor 2 (FGFR2) inhibitors, isocitrate dehydrogenases (IDH) inhibitors, BRAF inhibitors, etc [27].

1. Receptor tyrosine kinase inhibitors

Receptor tyrosine kinase (RTK) is a cytoplasmic membrane receptor protein (composed of extracellular ligand-binding domains, transmembrane helical domains, and intracellular domains) that mediates cell communication and signaling [28]. Although the etiology of ICC varies, abnormal activation of receptor tyrosine kinase signaling pathways remains a common mutation in ICC. In recent years, many novel targets for receptor tyrosinase inhibition have been proposed.

1.1. Fibroblast growth factor receptor inhibitors

Fibroblast growth factor receptor (FGFR) belongs to the RTKs family, which plays an important role in embryo development, tissue repair, tumor angiogenesis and proliferation [29]. FGFR is expressed in a variety of cell types and consists of four intracellular transmembrane receptors with tyrosine kinase domains (FGFR1-4) encoded by FLG, BEK, CEK-2, and FREK genes [30]. FGFR mutations are found in 10% to 15% of ICC [31]. FGFR mutations cause it to induce receptor dimerization through autophosphorylation at the C-terminal of the intracellular domain and other receptors or effector molecules involved in specific pathways of cell survival and proliferation, including Ras-MAPK, PI3K-Akt, PLCγ, and STAT [32,33].

Genomic studies of CCA have shown that approximately 15% of patients with are associated with abnormalities of FGFR2, while approximately 50% of tumors of CCA (intrahepatic, perihilar, and distal) have overexpression of FGFR4 [25,26]. FGFR inhibitors play an important role in ICC, and FGFR mutations are common in patients with CCA. This article summarizes the research progress of FGFR inhibitors (Table 1).

1.1.1. Pemigatinib

Based on the results of the Fight-202 trial, the highly selective FGFR1-FGFR3 inhibitor pemigatinib became the first FGFR inhibitor approved by the U.S. Food and Drug Administration for late-stage CCA with FGFR2 fusion or rearrangement. In this multicenter trial, 147 patients with locally advanced or metastatic disease who had failed at least one previous systemic therapy. The 107 of whom had FGFR2 fusion or rearrangement, were scheduled to take 13.5 mg pemigatinib orally once daily on the 1st to 21st days, taking off for 7 days, and 28 days as a treatment cycle [34]. The objective response rate (ORR) of second-line treatment was 35.5%, and the disease control rate (DCR) was 82.2%, the median progression-free survival (mPFS) was 6.9 months and the median overall survival (mOS) was 21.1 months. The most common adverse events (AE) were hyperphosphatemia (60%), a common side effect of FGFR inhibitors. Other less common adverse events include hypophosphatemia, arthralgia, stomatitis, hyponatremia, abdominal pain, and fatigue. Grade IIIor worse AEs occurred in 64% of patients, and hypophosphatemia was the most common in 12% of patients, while all hyperphosphatemia events were grade I or II [34]. It is particularly noteworthy that pemigatinib may not be suitable for trematode-associated CCA, as FGFR2 fusion is not found at a high rate in these tumors [35].

The Phase III trial of pemigatinib, FIGHT-302 (NCT03656536), will compare the efficacy and safety of pemigatinib with gemcitabine plus cisplatin in the treatment of advanced CCA patients with FGFR2 rearrangement.

1.1.2. Infigratinib

Infigratinib (BGJ398), a selective oral inhibitor of FGFR1-FGFR3 received accelerated U.S. FDA approval based on data from a single-arm Phase II trial for the treatment of previously treated patients with locally advanced or metastatic CCA with FGFR2 fusion or reconfiguration. A total of 122 patients, 108 with FGFR2 fusion and rearrangement and at least one systemic treatment, were enrolled in the clinical trial and were scheduled to receive 125 mg infigratinib for 1–21 days and 22–28 days of discontinuation. Infigratinib in these patients, second-line treatment ORR was 23.1%, DCR was 84.3%, mPFS was 7.3 months, and mOS was 11.8 months. Hyperphosphatemia, stomatitis, fatigue, and hair loss were the most common adverse events. Grade III or worse AEs occurred in 64% of patients, and six grade IV adverse events were laboratory abnormalities [36].

A first-line randomized Phase III PROOF study (NCT03773302) is currently underway to evaluate infigratinib versus gemcitabine plus cisplatin in patients with CCA. However, in recent clinical studies, acquired resistance mutations of FGFR2 including FGFR2 N549K/H, V564F, E565A, L617V/M, K641R, K659M and

Table 1. Clinical progress of FGFR inhibitors in cholangiocarcinoma.

Drug name	Disease	Stage	NCT NO.	Drug type	Indications	Experimental information	Result
Pemigatinib/ INC054828	ICC	Listed	–	FGFR1/2/3 inhibitors	CCA, especially CCA of FGFR2 fusion/ rearrangement	–	–
Infigratinib/ BGJ398	ICC/pCCA/ dCCA	III	03773302	FGFR2 inhibitors	Advanced cholangiocarcinoma/ FGFR2 gene mutation	48 patients (Multicenter, Open Label, 2:1 Randomized, Controlled Phase 3)	–
Futibatinib/ TAS120	ICC/pCCA/ dCCA	II	02052778	FGFR1/2/3/4 inhibitors	Advanced cholangiocarcinoma/ FGFR2 fusions/Gene rearrangement	386 patients with advanced solid tumors with and without genomic FGF/FGFR abnormalities were enrolled	Phase II clinical results are expected
Derazantinib/ ARQ087	ICC/HCC	II	03230318	Pan-FGFR inhibitor	ICC/ combined HCC and CCA	148 cases of inoperable or advanced CCA with FGFR2 mutation	Phase II clinical results are expected
TT-00420	ICC/pCCA/ dCCA	II	04919642	Multi-kinase inhibitors	CCA/FGFR2 fusion/FGFR2 gene mutation/FGFR1 alteration/FGFR3 alteration	80 patients with advanced/metastatic and surgically unresectable CCA	Phase II clinical results are expected
HMPL453	ICC	II	04353375	FGFR1/2/3/4 inhibitors	ICCA with FGFR2 fusion	Expect to enroll 29 patients with advanced/metastatic FGFR2 gene alteration who have failed at least one previous treatment	Phase II clinical results are expected
HH185/D185	ICC/pCCA/ dCCA	II	05039892	Pan-FGFR inhibitor	FGFR2 mutant CCA	Expect to enroll 50 patients with advanced/metastatic FGFR2 gene alteration who have failed at least one previous treatment	Phase II clinical results are expected
Lenvatinib/ E7080	ICC/pCCA	II	02579616/04211168	FGFR1, KIT, PDGFR and VEGFR1/2/3 inhibitors	Advanced CCA	29 patients with unresectable BTC who experienced disease progression or failure following a two-drug chemotherapy regimen with gemcitabine	ORR: 11.5% PFS:3.19 months OS:7.35 months DCR:84.6%
Gunagratinib	ICC	I / II	03758664	Pan-FGFR inhibitor	CCA resistant to first-generation FGFR inhibitors	56 patients with advanced solid tumors are expected to participate	Phase II clinical results are expected
E7090	ICC	I	04238715	FGFR1/2/3 inhibitors	CCA with FGFR2 mutations	60 patients with fusion of thecholangiocarcinoma with FGFR2 gene are expected to be enrolled.	Phase I clinical results are expected
RLY-4008	ICC	I / II	04526106	FGFR2 inhibitor	FGFR2 amplified, mutated, rearranged, translocated, and activated CCA	Expect to receive 125 patients with unresectable or unresectable metastatic ICC and other unresectable or metastatic solid tumors	Phase I clinical results are expected
Binimetinib	dCCA	II	05564403	FGFR inhibitor	Recurrent/ Unresectable dCCA	66 Patients with dCCA	–

K714R were found in patients treated with infigratinib [37,38].

1.1.3. Futibatinib

In 2018, the US FDA granted futibatinib the designation of an orphan drug (ODD) for the treatment of CCA. Futibatinib, an inhibitor of FGFR1-FGFR4 was granted breakthrough drug designation (BTD) by the US FDA based on data from this study. For the treatment of locally advanced or metastatic CCA previously treated with FGFR2 gene rearrangement, including gene fusion. In this study, 103 patients with FGFR2 gene rearrangement (including gene fusion) with ICC received futibatinib at a dose of 20 mg once daily. The ORR of futibatinib was 41.7%. The median duration of response (DOR) was 9.7 months, 72% were ≥6 months,

and the DCR was 82.5%. The mPFS was 9.0 months and the mOS was 21.7 months, with 72% of patients alive at 12 months. In terms of safety, common treatment-related adverse events (TRAE) were hyperphosphatemia, hair loss, and dry mouth. The most common grade III TRAE was hyperphosphatemia, which disappears with appropriate treatment. A case of grade IV transaminase elevation was reported with no treatment-related death.

1.1.4. Derazantinib

Derazantinib has received ODD for the treatment of ICC in the United States and the European Union. The latest analysis of the Phase II FIDES-01 study cohort 1 (ICC with FGFR2 gene fusion) showed an objective response rate (ORR) of 21.4%, a DCR of 74.8%, and an mPFS of 7.8 months. These clinical data further support the clinical utility of derazantinib monotherapy in CCA. In cohort 2 (FGFR2 gene mutation or amplification), the DCR was 79%, with one patient with a confirmed complete response to CR, one patient with a partial but unconfirmed response to PR, and 9 patients with stable SD and optimal response BOR [39]. Compared to other FGFR inhibitors, derazantinib was as effective as infigratinib in patients with CCA with FGFR2 mutations, but there was room for improvement compared to futibatinib and pemigatinib.

The summary of the research results confirms that the FGFR inhibitor targeted therapy has a certain curative effect for CCA patients, but the specific therapeutic effect needs more clinical research data to be confirmed.

1.2. Neurotrophic receptor tyrosine kinase inhibitors

Neurotrophic receptor tyrosine kinases (NTRK) are encoded by the NTRK1, NTRK2 and NTRK3 genes in the tropomyosin receptor kinases (TRK) family of transmembrane proteins TRKA(high affinity nerve growth factor receptor), TRKB (BDNF/NT-3 growth factor receptor) and TRKC (NT-3 growth factor receptor), plays a key role in physiology, development, and function of the peripheral and central nervous system [40]. The fusion of the NRTK gene with other genes will lead to a continuous active state of the TRK protein. It will trigger the reaction of the free activation and signal transduction cascade of intracellular biological pathways, and then lead to abnormal cell cycle progression, proliferation, apoptosis, and survival [41].

NTRK fusion is rare in ICC compared to 15% of patients with FGFR2 mutations [18]. The first-generation NTRK inhibitors larotrectinib (LOXO-101) and entrectinib (RXDX-101) have achieved good results in patients with positive NTRK fusion [42,43]. However, larotrectinib has a significantly shorter half-life (2.9 h) than enttritinib (20-22 h), which may affect the safety and efficacy of these drugs [44]. Similar to other tyrosine kinase inhibitors, first-generation TRK inhibitors can control the initial disease, but resistance caused by genetic mutations is still found in clinical use [42].

A second generation of TRK agents targeting drug resistance is in development and is currently being studied in a Phase I and Phase II study involving dose escalation and extension in children and adult cancer patients. Selitrectinib is an oral next-generation selective TRK inhibitor that remains potent in the presence of mutations in the TRK kinase domain. Selitrectinib showed strong binding to wild-type TRKA, TRKB, and TRKC (in kinase assay & LT; meanwhile, selitrectinib also showed low nanomolar inhibitory activity against TRK proteins with different resistance mutations [45]. Several other multikinase inhibitors, such as crizotinib, capbozanitinib, ponatinib, and nintedanib, have also shown some inhibitory activity against NTRK [43]. The research progress of NRTK inhibitors is shown in Table 2. Therefore, clinical studies of NRTK inhibitors can be increased and should focus on reducing drug resistance with improving drug efficacy in the future.

Table 2. Clinical progress of NTRK inhibitors in cholangiocarcinoma.

Drug name	Disease	Stage	NCT NO.	Drug type	Indications	Experimental information	Result
larotrectinib	ICC	Listed	–	TRK inhibitor	Solid tumors with NTRK fusion	–	–
entrectinib	ICC/pCCA/dCCA	II	02568267	TRK/ROS inhibitors	Solid tumors with NTRK fusion	534 patients	–
selitrectinib	ICC/pCCA/dCCA	I	03215511	TRK inhibitors	Solid tumors with NTRK fusion	81 adults and children previously treated for NTRK fusion cancer	Clinical trial results are expected

1.3. HER inhibitors

Abnormalities in human epidermal growth factor receptor (HER) tyrosine kinase include mutations in EGFR and HER1-4. EGFR is a subclass of tyrosine kinase transmembrane receptors that bind to epidermal growth factor and activate signaling pathways such as cell movement, cell adhesion, angiogenesis, and invasion. EGFR targets two types of drugs: small molecule tyrosine kinase inhibitors that act through intracellular pathways, such as erlotinib and geitinib; another group is monoclonal antibodies that work through an extracellular pathway, such as cetuximab and panitumumab [39]. In the phase III clinical trial of erlotinib (NCT01149122), a total of 133 patients with advanced CCA were enrolled, and the efficacy of erlotinib combined with GEMOX chemotherapy (gemcitabine + oxaliplatin) and GEMOX chemotherapy alone in the treatment of advanced CCA was compared. The results showed that, the mPFS was 4.2 months in the GEMOX chemotherapy group alone, and 5.8 months in the erlotinib combined with the GEMOX chemotherapy group. The objective sustained release rate of the erlotinib combined with the GEMOX chemotherapy group was significantly higher than that of the chemotherapy group (30% vs. 16%), but the overall survival of the two groups did not prolong. The median survival was 9.5 months [46]. In a phase II clinical trial of cetuximab, a total of 150 patients with advanced CCA were enrolled. The efficacy of cetuximab combined with GEMOX chemotherapy and GEMOX chemotherapy alone in the treatment of advanced CCA was compared. The results showed that the mPFS of the chemotherapy alone group was 5.5 months. The median progression-free period of cetuximab combined with GEMOX was 6.1 months, but the mOS of cetuximab combined with GEMOX was significantly lower than that of chemotherapy alone (11.0 months vs.12.4 months) [47]. There were also reports of 63% objective sustained release rate in phase II clinical trials, in which 3 patients achieved complete remission and 9 patients successfully underwent down-stage surgery after treatment [48]. At present, there is no unified conclusion on the efficacy of chemotherapy alone for this type of drugs. In the phase II clinical trial (NCT00948935) of panizumab in combination with gemcitabine and irinotecan in the treatment of advanced CCA, a total of 35 patients were enrolled. The results showed complete responses in 2 patients and partial responses in 9 patients, with a 5-month progression-free survival rate of 5 months of 69%, a sustained remission release rate of 31%, and a mOS of 12.0 months [49].

Inhibitors targeting HER include lapatinib, trastuzumab, and pertuzumab, and the safety and effectiveness of HER inhibitors are gradually tested in early clinical trials. And anti-HER treatment may bring new treatment opportunities to CCA patients with HER amplification or overexpression.

2. Isocitrate dehydrogenase inhibitors

Isocitrate dehydrogenase (IDH) is a key enzyme in the tricarboxylic acid cycle, catalyzing oxidative decarboxylation of isocitrate to α-ketoglutarate (α-kg) and reducing NADP + to NADPH [50]. When IDH gene mutation occurs, a large amount of tumor metabolite 2-hydroxyglutaric acid (2-Hg) is deposited, while the activity of α -ketoglutaric acid (α-kg) is inhibited [51]. Then it leads to abnormal histone and DNA methylation, resulting in gene expression disorders, resulting in tumor [52]. IDH mutations occur in about 10-28% of ICC [53], IDH1 gene abnormalities were more common than IDH2 gene abnormalities [54]. The progress of IDH inhibitor research is shown in Table 3.

2.1. Ivosidenib

Ivosidenib, a targeted inhibitor of IDH1 mutations, is approved for newly diagnosed and relapsed or refractory IDH1-mutated acute myeloid leukemia (AML) that cannot receive intensive chemotherapy and for orphan drug designation. IDH1 inhibitor ivosidenib has been granted priority review by the US FDA based on the results of the international randomized Phase III ClarIDHy study. The trial evaluated CCA patients with advanced IDH1 mutations who had failed first-line chemotherapy compared to placebo treatment. Of the 185 patients with advanced CCA who had received at least second-line therapy and carried IDH1 mutations, 126 were treated with 500 mg ivonib for 2.7 months of mPFS (1.4 months in placebo). The incidence of PFS at 6 and 12 months for ivosidenib was 32% and 22%, respectively, and the mOS was 10.8 months (6.0 months after adjustment for placebo). The ORR of the avonib group was 2%, including 3 PR cases and 63 SD cases. None of the patients in the placebo group achieved objective response, and 17 patients had SD. The DCR was 53% and 28%, respectively. The common adverse reactions in ivonib group were ascites, nausea, fatigue, diarrhea, etc., and the overall tolerance was better [55].

2.2. Enasidenib

Enasidenib, an inhibitor of IDH2 mutations, is the first anticancer drug that targets tumor metabolism and is approved by the US FDA in 2017 for newly

Table 3. Clinical progress of IDH inhibitors in cholangiocarcinoma.

Drug name	Disease	Stage	NCT NO.	Drug type	Indications	Experimental information	Result
ivosidenib/ AG-120	ICC/pCCA/ dCCA	III	02989857	IDH1 inhibitor	Advanced/ metastatic CCA	187 Patients with advanced cholangiocarcinoma with IDH1 mutations who had received one but not more than two systemic therapies	PFS:2.7 months vs1.4 months Other experimental results have not yet been reported
AB-218 capsule	ICC/pCCA/ dCCA	I	05814536	IDH1 inhibitor	CCA with IDH1 mutation	63 Patients with IDH1 Mutation	Phase I clinical results are expected
dasatinib	ICC/pCCA/ dCCA	II	02428855	IDH1 inhibitor	Advanced/ metastatic CCA	8 Patients	–
enasidenib/ AG-221	ICC	I/II	02273739	IDH2 inhibitor	IDH2 abnormal solid tumor	21 Adults with AITL with advanced solid tumors (including gliomas) or isocitrate dehydrogenase-2 (IDH2) mutations	–
BAY-1436032	ICC/pCCA/ dCCA	I	02746081	IDH1 inhibitor	Solid tumors with abnormal IDH1	81 patients with advanced solid tumors with IDH1-R132X mutations were treated	Phase I clinical results are expected
IDH305	ICC	I	02977689	IDH1 inhibitors	Solid tumors with abnormal IDH1	The experiment has been withdrawn	–
GSK321		NOT		IDH1 inhibitors	Solid tumors with abnormal IDH1	–	–
GSK864		NOT		IDH1 inhibitors	Solid tumors with abnormal IDH1	–	–

NOT: Not entered clinical practice.

diagnosed and relapsed or refractory acute myeloid leukemia (AML) of the IDH1 mutant that cannot receive intensive chemotherapy. A phase I/II clinical trial of mIDH2 is currently underway in solid tumors (NCT02273739), but the experimental results have not been disclosed [56].

IDH inhibitors can inhibit the aberrant enzyme activity produced to block the proliferation of CCA tumor cells by mutations in the IDH gene, and induce tumor cell apoptosis and enhance immune surveillance.

3. BRAF kinase inhibitors

BRAF is a serine/threonine protein kinase that belongs to the RAF protein family, and is involved in signal transduction through the MAPK pathway to stimulate cell growth and survival. Mutations in the BRAF gene (V600E) lead to activation of kinase triggering sustained activation of the signaling pathway that promotes tumorigenesis. BRAF mutations often occur in ICC, with KRAS mutations occurring in 8.6 – 24.2% ICC and BRAF mutations occurring in 3 – 7.1% ICC. Ras-Raf-Mek-Erk signaling pathway is often abnormally expressed [14]. Currently, there are no direct effective inhibitors against KRAS mutations, and the main treatment is to inhibit KRAS downstream proteins. Vemurafenib and dabrafenib are targeted inhibitors of V600E. Selumetinib, binimetinib, and trametinib are targeted inhibitors of MEK. In a phase II basket trial of vemurafenib, the ICC response rate was only 12.5% [57]. There may be many patients who have previously received anti-EGFR antibody therapy, leading to the unsatisfactory remission rate of ICC in this study. More studies are needed to demonstrate the therapeutic efficacy of such drugs. In the Phase II trial of dallafenib in combination with trimeitinib (MEK inhibitor), the overall response rate was 51%, the median PFS was 9 months, and the mOS was 14 months [58], which was comparable to gemcitabine plus cisplatin as first-line treatment.

4. Others

In addition to the targets described above, several CCA-related targets are still in the early stages of research. ICC is prone to frequent chromatin inactivation. BAP1 encodes a nucleic acid deubiquitylation enzyme for chromatin remodeling, and subunits of the chromatin remodeling complex are ARID1A and PBRM1 [59]. There are two clinical studies on inhibitors of chromatin remodeling complexes. One is histone deacetylation (HADC) inhibitors, such as romidepsin, vorinostat, and valproic acid. The other is methyltransferases such as azacitidine and decitabine [54]. At present, there is no clinical evaluation of the efficacy of these drugs for CCA, which may become a new target for CCA therapy.

Abnormal Janus kinase (JAK)/STAT activation is observed in approximately 50% of CCA patients, while STAT3 overactivation was more common in ICC [60]. The spHK-2 inhibitor opaganib (Yeliva, ABC294640), activated by inhibiting STAT3 phosphorylation, initially showed positive efficacy against CCA in the Phase I clinical trial (NCT01488513). Opagani alone in the treatment of advanced CCA in a single-arm phase II study (NCT03377179) has met the pre-set efficacy goal (i.e. at least 1 response in 12 patients), and is currently being enrolled and evaluated for Opagani alone or in combination with hydroxychloroquine sulfate.

A phase II clinical trial of the anti-vascular endothelial growth factor receptor (VEGFR) monoclonal antibody bevacizumab combined with GEMOX (gemcitabine + oxaliplatin) regimen included 35 patients, the results showed that the 6-month PFS was 63%, although lower than the prespecified value of 70% in the study, but still higher than the GEMOX group alone [61]. In another multicenter phase II clinical trial involving 39 patients with advanced biliary tract carcinoma (BTC), the treatment with bevacizumab combined with GEMCAP (gemcitabine + capecitabine) showed that its DCR up to 72%, the mPFS was 8.1 months and the mOS was 10.2 months [62]. Ramucirumab is an anti-VEGFR-2 monoclonal antibody. At the 2018 ASCO Annual Meeting, the results of its phase II clinical trial of second-line treatment in the field of BTC were reported. A total of 57 patients were included in the study. The ORR was 0%, the DCR was 44%, and the mPFS and mOS were 2.73 and 6.31 months, respectively. The results were similar to the value of second-line chemotherapy and the patients were well tolerated.

Multi-targeted tyrosine kinase inhibitors (mTKIs) have also been actively explored in the field of ICC. The value of regorafenib in the second-line treatment of advanced BTC is worthy of further study and discussion, which is mainly due to the following two clinical studies: a phase II clinical trial that included 39 patients with advanced BTC, mPFS, and mOS were 3.7 and 5.4 months, the 1-year OS was 35.9% [63]; another phase II clinical trial of regorafenib showed similar results, with mPFS of 15.6 weeks, mOS of 31.8 weeks and 1-year OS of 40% [64]. Similar to regorafenib, China's self-innovated TKI drug surufatinib also has dual mechanisms of anti-angiogenesisand promotion of immune response, and can act simultaneously on VEGFR-1/2/3, FGFR-1 and the colony stimulating factor 1 receptor (CSF-1R). Based on this, surufatinib can not only inhibit tumor growth by inhibiting tumor angiogenesis, but also regulate tumor immune system by inhibiting CSF-1R. Surufatinib has also achieved good results in the BTC field in 2021. The results of the phase II clinical study of its single drug for the second-line treatment of advanced BTC showed that the 16-week PFS was 46.33%, the m PFS was 3.7 months and the mOS was 6.9 months, showing good efficacy and safety [60].

A latest trail named TOPAZ-1 study (NCT03046862) evaluates the gemcitabine and cisplatin plus durvalumab with or without tremelimumab as first-line treatment in patients with advanced CCA [65]. Durvalumab is an IgG1 monoclonal antibody that selectively binds to PD-L1. The results showed that durvalumab significantly improved the efficacy and acceptable safety of gemcitabine and cisplatin plus in patients with CCA.

In addition, there are some provoking studies on the treatment of CCA in the preclinical stage. Many cancer-associated fibroblasts (CAFs) in tumor tissue build a good environment for the development of tumors. Mertens et al. found that the occurrence of death in CAFs is in part due to up-regulation of the pro-apoptotic protein Bax. Treatment with the cytotoxic drug navitoclax (a BH3 mimetic) treatment can trigger CAFs apoptosis and inhibit CCA tumor growth and survival [66]. Cadamuro et al. found platelet-derived growth factor D (PDGF-D) stimulates fibroblasts to produce VEGF-C and VEGF-A, which leads to the expansion of the lymphatic vasculature and intracellular infiltration of tumor cells of CCA. Inhibition of PDGF-D can reduce lymphatic vascularization and lymph node metastasis-associated CCA [67]. Many studies indicated that the changes of extracellular matrix (ECM) in biochemistry, biomechanics, structural composition and distribution in cancers and ECM would increase rapidly in CCA. By regulating the components or key targets of the ECM, such as type III collagen and matricellular proteins, the therapeutic effect of CCA could be achieved [68–70]. Meanwhile, Yoo et al. found that the oncolytic vaccinia virus (CVV) may be a novel method of treating CCA [71].

In conclusion, more and more relevant clinical studies provide new directions and hopes for the therapy of CCA. In this process, it needs to pay attention to the impact of individual variability, and should update and adjust the protocol with the latest experimental results.

5. The combination therapy of targeted therapy and immunotherapy

Nowadays, immune checkpoint inhibitors (ICIs) have achieved significant clinical efficacy in tumor patients. The combination therapy of targeted therapy and

immunotherapy has become a new hot topic in CCA research. Two clinical studies (NCT03797326, NCT03895970) showed that pembrolizumab combined with lenvatinib can be used as a back-line exploratory treatment option for non-resectable or progressive biliary tract malignancies [72,73]. A multicenter randomized phase II study showed that the combination therapy of atezolizumab and cobimetinib was effective in patients with advanced CCA who had previously received first/second line treatment. The mPFS of the combined drug group was 3.65 months and that of the single drug group was 1.87 months [74]. Zhou reported at the 2020 ESMO that the results of the study (NCT03951597) of toripalimab combined with lenvatinib and GEMOX chemotherapy for the first-line treatment of non-resectable advanced ICC showed that the ORR was 80% and the DCR was 93.3% (28/30), of which 3 cases were successfully transformed and the tumor was surgically removed. In 2020 ESMO, Zhang found that GEMOX combined with donafenib and tislelizumab as first-line treatment for locally advanced or metastatic BTC showed controllable toxicity and encouraging efficacy, especially in terms of promising conversion rates in Phase III patients. The combination therapy of CCA has made great progress in recent years, and there are many clinical trials of different combination regimens under exploration. However, there are still many key scientific and clinical issues that need to be explored. The anti-tumor activity of ICIs in CCA is limited, which indicates the need for more in-depth research on immunosuppressive cell populations.

6. Conclusions

The emergence of targeted therapy has promoted the precise treatment of CCA. According to the stratification of biomarkers, patients are treated with corresponding targeted drugs at the molecular level. Targeted therapy targets specific molecular markers that are enriched in tumor cells and have key driving value, which influences certain types of tissues and cells. It has a specific anti-tumor effect and significantly reduces damage to normal cell. In conclusion, targeted therapy has a broad application prospect in the field of CCA treatment. Currently, there are an increasing number of targeted drugs for CCA, especially with the marketing of the FGFR inhibitors infigratinib and pemigatinib and the priority evaluation of the IDH inhibitor ivosidenib, for patients with metastatic or unresectable ICC. Targeted therapy is likely to become a new, widely accepted therapeutic mode in the future. But there are still many problems need to be solved, such as low mutation rate of genetic testing, drug resistance, and expensive targeted drugs. In the future, researches should be devoted to actively addressing the challenges of targeted therapy, improving the efficacy and individualization, in order to better benefit patients. It is believed that with the continuous development of gene sequencing technology and the development of targeted therapy combined with other treatment, there will be more effective targeted therapy and combination therapy methods to benefit patients with CCA to improve the prognosis of patients.

Authors' contributions

Yuhang Li and Jianfeng Yu contributed to the completion of data and wrote the main manuscript text. Yuhang Li contributed to making the figure. Jianfeng Yu contributed to making the tables. Yuhang Li, Yujing Zhang, and Chuang Peng contributed to the conception of the study. Jianfeng Yu, Yinghui Song, and Sulai Liu helped perform the analysis and participated in constructive discussions. All authors reviewed and approved the final manuscript.

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