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Current status of targeted and immunotherapy for tumors of the biliary system

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ABSTRACT

Cancers of the biliary tract (BTCs), comprising intrahepatic, perihilar, and distal cholangiocarcinomas along with gallbladder carcinomas, persist as clinically complex oncological entities characterized by constrained treatment modalities and unfavorable clinical outcomes. Contemporary genomic characterization has revealed druggable genomic aberrations such as IDH1/2 gene mutations, FGFR2 rearrangements, and HER2 amplification events, creating opportunities for precision interventions. Specifically, fibroblast growth factor receptor inhibitors (e.g., pemigatinib, infigratinib) and isocitrate dehydrogenase-1 inhibitors (e.g., ivosidenib) have exhibited statistically significant clinical benefits in molecularly defined patient subgroups, subsequently obtaining therapeutic indications from regulatory agencies. Regarding immunotherapeutic approaches, programmed death-1/programmed death-ligand 1 blockade agents demonstrate limited efficacy in single-agent applications, with objective response rates ranging from 10% to 20%. Current translational research prioritizes multimodal therapeutic approaches integrating immune checkpoint inhibitors with cytotoxic chemotherapy, angiogenesis inhibitors, or novel immunostimulatory agents to potentiate antitumor immune responses. Biomarkers like tumor mutational burden, microsatellite instability, and PD-L1 expression are being explored to predict therapeutic outcomes. Despite progress, challenges persist, including primary resistance mechanisms, tumor heterogeneity, and the need for improved preclinical models. This review synthesizes current evidence on targeted and immunotherapeutic approaches in BTCs, emphasizing the integration of precision medicine, biomarker-driven trials, and novel combination strategies to optimize clinical outcomes. Future research should focus on overcoming resistance, elucidating the tumor microenvironment's role, and expanding access to molecular testing to personalize treatment for this aggressive disease

KEYWORDS

Biliary tract tumors; Immunotherapy; Targeted therapy

1 Introduction

Biliary tract malignancies represent clinically aggressive neoplasms with marked molecular heterogeneity, arising from the epithelial lining of the bile duct system and gallbladder. Over 90% of cases manifest as adenocarcinomas, demonstrating dismal prognosis with median overall survival not exceeding 5 years in >95% of cases. These neoplasms are anatomically stratified into: (1) intrahepatic cholangiocarcinoma, (2) perihilar cholangiocarcinoma, (3) distal cholangiocarcinoma, (4) gallbladder carcinoma, and (5) periampullary carcinomas. Characterized by asymptomatic progression, >70% of patients present with locally advanced or metastatic disease at diagnosis, precluding curative-intent resection [1]. While therapeutic advances have remained incremental in advanced-stage management, persistent investigative efforts continue to redefine treatment paradigms.

Contemporary oncological practice has witnessed molecularly-guided precision therapeutics and immunomodulatory strategies revolutionize treatment landscapes across multiple solid tumors. Mechanistic studies have provided critical insights into the molecular pathogenesis of biliary malignancies, particularly the roles of somatic driver mutations, dysregulated oncogenic pathways, and tumor microenvironment-mediated immunosuppression. These discoveries have catalyzed the development of targeted biological agents and combinatorial immunotherapeutic regimens. This comprehensive review synthesizes recent progress in targeted therapeutics and immune-based interventions specific to gallbladder carcinoma, with particular emphasis on biomarker-driven clinical trial outcomes..

2 Molecular diagnosis of biliary tract tumors

The primary varieties of biliary malignancies are malignant epithelial tumors in the biliary tract, predominantly consisting of adenocarcinoma in the bile ducts or gallbladder, These are categorized into intrahepatic bile ducts, gallbladder, and extrahepatic bile ducts based on various tumor locations, while intrahepatic bile ducts fall into several types: bold ductal; small bile duct; undifferentiated carcinoma; mixed hepatocellular-intrahepatic cholangiocarcinoma; neuroendocrine tumors; large-cell neuroendocrine carcinoma; small-cell neuroendocrine carcinoma; and mixed neuroendocrine-non-neuroendocrine tumors. Subsequently, the gallbladder and extrahepatic bile ducts are segmented

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into various types: adenocarcinoma (nonspecific, intestinal), clear cell adenocarcinoma, mucinous cystic tumor-associated invasive carcinoma, mucinous adenocarcinoma, intracystic/intraductal papillary tumor-associated invasive carcinoma, squamous cell carcinoma, undifferentiated carcinoma, adenosquamous carcinoma (with a squamous carcinoma component exceeding 25%), neuroendocrine tumors, large-cell neuroendocrine carcinoma, small-cell neuroendocrine carcinoma, and mixed neuroendocrine-nonneuroendocrine Tumors.

The genetic variation and heterogeneity in biliary cancers are intricately linked to multiple factors such as the sites of tumor origin, epidemiological risk elements, and clinical-pathological characteristics. Utilizing high-throughput sequencing techniques, numerous researches have documented the genetic changes in biliary tract tumors at various origins, including FGFR2 fusion, mutations IDH1/2 and BRAFV600E in intrahepatic cholangiocarcinomas, and TP53, KRAS, and BRCA1 mutations in extrahepatic cholangiocarcinomas, along with ERBB2 amplification in biliary tract tumors. Amplification of ERBB2 occurs more frequently in cases of gallbladder cancer . In addition, the molecular features of biliary malignant tumors vary even in the same biliary system region, with IDH1/2 mutations and FGFR2 fusion variants usually being rare in the bold ductal pathology subtype of intrahepatic cholangiocarcinoma, while the above features are more common in the small ductal pathology subtype of intrahepatic cholangiocarcinoma [2]. Moreover, epidemiological factors also have an impact on the molecular characteristics of biliary malignancies . Several drugs have been approved for clinical targeted therapy of biliary tract malignancies or other solid tumors in China. The frequency of molecular target variants and detection methods related to targeted therapy for biliary malignant tumors are summarized in the following table [3].

Table 1 Molecular target variation related to targeted therapy of biliary tract malignancies

molecular characterization	Frequency of intrahepatic cholangiocarcinoma variants		Frequency of extrahepatic cholangiocarcinoma variants	
	Europe and America	China	Europe and America	China
molecular characterization	5.5~16.0(%)	5.5~12.5(%)	0	0
FGFR2 fusion/rearrangement	19~30(%)	6.5~20(%)	0~5.4(%)	0~8.7(%)
IDH1 mutation	3~7(%)	1(%)	1~3(%)	8(%)
BRAFmutation	3~3.7(%)	8(%)	1.3~11.0(%)	5~6(%)
ERBB2 (HER2) mutation/overexpression	1.2~3.6(%)	2(%)	-	-
NTRK1-3 Fusion/Rearrangement	1.1(%)	1.8(%)	-	-
RET fusion/rearranging	<1(%)	<2.3(%)	<1(%)	<2.3(%)
KRAS mutation	2~5(%)	1~30(%)	2.1~3.7(%)	

molecular characterization	Frequency of gallbladder cancer variants		Detection Methods
	Europe and America	China	
FGFR2 fusion/rearrangement	0~3(%)	0~1.7(%)	FISH/sequencing of genome
IDH1 mutation	0~1.5(%)	0.5~1.7(%)	sequencing of genome
BRAFmutation	1(%)	5.9(%)	PCR/sequencing of genome
ERBB2 (HER2) mutation/overexpression	8.3~16.0(%)	13.3~14.8(%)	IHC/FISH/sequencing of genome
NTRK1-3 Fusion/Rearrangement	-	1.7(%)	FISH/PCR/sequencing of genome
RET fusion/rearranging	-	-	FISH/sequencing of genome
KRAS mutation	<1(%)	<2.3(%)	PCR/sequencing of genome
PTEN mutation	2~5(%)	0~57(%)	IHC/sequencing of genome

A range of biomarkers, such as PD-L1 protein expression, tumor mutation burden, mismatch repair-deficiency, and microsatellite instability, are linked to the effectiveness of immunotherapy in treating biliary malignancies, as evidenced by various studies on immunotherapy-related molecular markers. Numerous biomarkers, such as TMB, mismatch repair-deficiency (dMMR), and microsatellite instability (MSI), are linked to the effectiveness of immunotherapy in treating solid tumors, with multiple studies on immunotherapy-related molecular markers noted in biliary tract cancers. [4].

3 Targeted therapies

3.1 Epidermal growth factor (EGFR) inhibitors

EGFR is the expression product of the proto-oncogene human epidermal growth receptor factor 1 (HER-1). Studies have shown that 38% to 100% of BTC cells express EGFR [5].There are two primary categories of EGFR inhibitors: a type of monoclonal antibodies like cetuximab and panitumumab, and a different type of small-molecule tyrosine kinase inhibitors, including erlotinib and gefitinib, among others. While EGFR inhibitors in treating advanced BTC have demonstrated anti-cancer properties, they are not supported by phase III studies that verify extended patient survival. Within a subset analysis of clinical trials involving 89 patients[6], Individuals suffering from intrahepatic cholangiocarcinoma and undergoing monotherapy might experience a survival advantage over the control group (15.1

vs. 11.8 months, P=0.13). Current phase II randomized controlled trials have been unable to verify whether the amalgamation of EGFR inhibitors and chemotherapy enhances patient survival rates.[6-7].

3.2 FGFR inhibitors

FGFR is a typical class of receptor tyrosine kinases, and its family includes four receptors (FGFR1, 2, 3, and 4) with a wide variation in distribution within human tissues, with FGFR2 rearrangements or fusions concentrated in intrahepatic cholangiocarcinoma . Infigratinib (BGJ398) functions as a selective, orally administered inhibitor of pan-FGFR kinase. A second phase of clinical testing[8] enrolled 61 patients with advanced cholangiocarcinoma with FGFR mutations, and BGJ398 was administered after the failure of first-line chemotherapy, with an RR of 14.8%, a DCR of 74.5%, and a median progression free survival (mPFS) of 5.8 months, showing a favorable anti-tumor effect and a controllable safety. Two related phase II clinical trials of ponatinib, another FGFR inhibitor, are underway.

3.3 IDH Gene Inhibitors

IDH, a crucial enzyme in the tricarboxylic acid cycle, facilitates the oxidative decarboxylation of isocitric acid, resulting in α-ketoglutarate (α-KG). This enzyme not only contributes to the metabolism of substances but also plays a role in controlling several key intracellular signaling routes. Altered IDH is capable of transforming α-KG into 2-hydroxyglutarate (2-HG). The primary cause of IDH mutation carcinogenesis is thought to be the suppression of α -KG-dependent dioxygenase activity by the altered IDH product, 2-HG. Within cholangiocarcinoma, mutations in IDH1/IDH2 show a notable specificity towards intrahepatic cholangiocellular carcinoma, occurring in 23% of cases; these mutations are absent in extrahepatic cholangiocellular carcinoma and gallbladder carcinoma . During the initial phase of trials, Ivosidenib (AG120), an oral inhibitor of IDH1, showed good tolerability in advanced cholangiocarcinoma patients with IDH1 mutations without any dose-limiting toxicity. The Lancet Oncology conducted a third-phase clinical trial on Ivosidenib to treat advanced IDH1-mutated cholangiocarcinoma post-chemotherapy. In ClarIDHy, Ivosidenib notably extended patient progression-free survival (PFS) to 2.7 months, overall survival (OS) to 10.8 months, and decreased disease progression or mortality risk by 63%. [9].

3.4 Inhibitors of Human epidermal growth factor receptor 2

(HER-2):

HER-2 overexpression and gene amplification were most common in gallbladder cancer (19%), with a higher rate of HER-2 overexpression in extrahepatic cholangiocarcinomas (17.4%) compared to intrahepatic cholangiocarcinomas (4.8%). According to Javle[10], administering HER-2-directed treatments (trastuzumab, patuzumab, or lapatinib) to nine gallbladder patients and five cholangiocarcinoma patients led to total remission in one, partial remission in four, and stable disease in three. This indicates the potential positive impact of trastuzumab on gallbladder cancer, warranting additional investigation.

3.4 Anti-angiogenic drugs

VEGF is expressed in 42% to 76% of cholangiocellular carcinomas . The monoclonal antibody bevacizumab and the small molecule tyrosine kinase inhibitors regorafenib and cediranib are among the most frequently utilized antiangiogenic medications.. Bréchon et al. found [11] found that the median PFS in the GEMOX (gemcitabine and oxaliplatin regimen) in combination with bevacizumab group and in the GEMOX regimen alone group were 6.48 months and 3.72 months, respectively (p=0.049) . The median OS was 11.31 and 10.34 months, respectively, and a related study by Valle et al [12] showed that small molecule tyrosine kinase inhibitors did not provide additional survival benefit to patients. In the cediranib group, the average duration of survival without disease progression was 8.0 months (95% CI 6.5-9.3), compared to 7.4 months (5.7-8.5) in the placebo group. (HR 0.93,95% CI 0.65-1.35; p=0.72).

4 Immunotherapy

Preliminary clinical research indicates that both tumor vaccines and explicit immunotherapy may offer anti-tumor benefits against biliary system tumors, yet recent findings haven't pinpointed any extra survival advantages. Presently, the focus of immunotherapy for tumors in the biliary system is on inhibitors of immune checkpoints. In cholangiocellular carcinomas, particularly intrahepatic ones, there's an increased expression of PD-1/PD-L1, frequently linked to unfavorable outcomes, indicating the potential efficacy of biliary system tumors in specific immunotherapy treatments[13-14]. Studies have shown that PD-1 monoclonal antibody in combination with immunomodulators may

improve efficacy [15].Robin and others. At the 2018 ASCO Congress, initial findings were disclosed from a phase II clinical study on the use of pembrolizumab alongside granulocyte colony-stimulating factor (GM-CSF) in treating advanced cholangiocarcinoma. This research included 24 individuals suffering from advanced cholangiocarcinoma who either advanced or developed resistance following more than one conventional treatment. In the research, the prescribed treatment involved administering PEM 200 mg intravenously every 21 days, followed by two rounds of GM-CSF 250 μg SC D1 through 14 Q21 days (during the second and third cycles or the first and second cycles). Initial findings indicated the presence of 5 PRs, accompanied by an Odds Ratio (ORR) of 21%. The study revealed the safety and acceptability of PEM in conjunction with GM-CSF for treating advanced cholangiocarcinoma.

The effectiveness of nabumab, a different PD-1 antibody, was assessed in 54 patients with advanced BTC who had undergone prior treatment [16]. Initial findings were disclosed at the 2019 ASCO, where 45 patients were evaluated for treatment success, with 22% experiencing partial remission and 38% deemed to have stable disease. Initial research indicates that immunotherapy exhibits anti-tumor properties in biliary tract tumors, with manageable side effects, suggesting its wide-ranging potential in treating these tumors.

5 Targeted combination chemotherapy

A prospective study [17] explored the role of cetuximab in combination with Gemox regimen in the treatment of BTC, in which the ORR was 63% and 9 (30%) patients (5 ICC) underwent downstaging surgery, with a median PFS of 21.2 (12.5-29.8) months for those who underwent downstaging surgery, and only 6.8 (4.5-9.1) months for those who did not undergo surgery. Median OS was not yet reached in those with downstage surgery and 15.2 (9.9-20.5) months in those without surgery. Another study explored the efficacy of the VEGFR inhibitor cediranib (Cediranib) in combination with a GC regimen versus GC regimen-only chemotherapy in patients with advanced BTC (ABC-03), with an ORR of 44% for the cediranib-combined GC regimen versus 19% for the GC-only chemotherapy group . Two cases of CR (3%) and 24 cases of PR (41%) were obtained in the cediranib combined with GC regimen group, while only 10 cases of PR (19%) were obtained in the GC regimen group, and no CR patients were seen.

6 Immunization combination chemotherapy

Findings from the TOPAZ-1 research indicated the superiority of dovarizumab combination chemotherapy (GC) over sole chemotherapy, as it decreased mortality risk by 24% and extended the median overall survival to 12.9 months (12.9 vs. 11.3), leading to a twofold increase in the three-year Overall Survival rate (14.6% vs. 6.9%), enhancing the average Progression-Free Survival to 7.2 months (7.2 vs. 5.7), diminishing the likelihood of disease advancement by 25%, enhancing ORR by 43%, accelerating the commencement of treatment, and maintaining a positive safety record, highlighting the benefits of this treatment plan. The KEYNOTE-966 research assessed the effectiveness of combining pabolizumab with chemotherapy (GC) against a placebo with GC in treating patients with advanced or inoperable BTC. Findings indicated that the combination of pabolizumab and GC markedly extended the median overall survival (OS) (12.7 vs. 10.9 months, HR=0.86, yet no notable disparities were observed in PFS (6.5 vs. 5.6 months), ORR (28.7% versus 28.7%) alongside TTR.

7 Immunization combined with targeted therapy

Current research is delving deeper into the use of anti-angiogenic medications and immune checkpoint inhibitors for BTC translational treatment. The SAGC study, a forward-looking phase II study, investigated the effectiveness of the initial treatment for advanced BTC using a regimen of sindilizumab, amilorotinib, and GC. A total of 80 patients were randomly distributed between the SAGC and GC regimen groups in a 1:1 ratio, with both groups undergoing 8 treatment cycles. The median patient count in each group was 1:1, and both groups experienced identical treatment rates. Both patient groups underwent eight treatment cycles, with an average monitoring period of 13.4 months. The SAGC group experienced a median progression-free survival (PFS) of 8.6 months, while the GC group had a median follow-up of 6.2 months (HR= 0.368, P<0.01). The odds ratios (ORRs) for the SAGC and GC groups were 52.8% and 29.4%, respectively, indicating that the initial treatment of advanced BTC using the SAGC regimen, as opposed to the GC regimen, markedly enhanced patient PFS and ORR, and the safety profile was acceptable. Compared to the GC regimen, the SAGC regimen markedly enhanced the progression-free survival (PFS) and overall response rate (ORR) of patients for initial treatment of advanced BTC, and given its acceptable safety record, it offers an innovative approach for the translational management of advanced BTC. A separate phase II single-arm, open-label clinical trial investigated the initial treatment for advanced BTC using amilorotinib and bemosubaisumab (PD-L1 monoclonal antibody) alongside albumin vincristine and cisplatin, involving

14 patients with an ORR of 42.8%, a DCR of 92.9%, and an unachieved median PFS, demonstrating initial effectiveness and tolerable side effects. The ZSAB- TransGOLP study [18], a single-arm, multicenter phase II investigation, assessed the effectiveness and safety of tirilizumab combined with lenvatinib and GEMOX in treating advanced BTC. Findings indicated a 43.9% ORR, 48.8% R0 resection rate, 87.8% DCR, and 9.1% pCR rate, validating the effectiveness and safety of this treatment for locally advanced BTC. The AK117-202 study [19], an open-label, multicenter, phase II trial, assessed ivosizumab (a PD-1/VEGF dual-antibody) alongside GC regimen. The first-line treatment for advanced BTC demonstrated an ORR of 63.6%, a DCR of 100%, a PFS of 8.5 months, and an OS of 16.8 months, highlighting its high anti-tumor efficacy and controlled safety, paving the way for initial treatment of advanced BTC.

8 Summary and Prospect

Numerous clinical studies have been carried out to assess the effectiveness of various specific agents in treating advanced tumors of the biliary system. However, the diverse clinical biology and molecular characteristics of these tumors, coupled with the scarcity of frequently occurring driver genes and limited positive outcomes, have posed significant challenges in clinical research. Presently, while certain single-arm clinical trials indicate that medications focusing on the EGFR and HER-2 pathways, along with multi-targeted anti-angiogenic drugs, MEK inhibitors, and other individual agents, exhibit anti-tumor effects against advanced BCT in backline treatments, a small segment of the patient group benefits, with their overall survival advantage still unverified by phase III studies. Presently, the amalgamation of EGFR, anti-angiogenic medications, and chemotherapeutic drugs hasn't enhanced the effectiveness of primary treatment. Certain medications targeting recently identified targets (like FGFR, IDH-1/2) show promising potential for use in clinical settings.

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