Current biologics for treatment of biliary tract cancers

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Current biologics for treatment of biliary tract cancers

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Abstract: Biliary tract cancers (BTC) is a group of malignancies that arise from the epithelial cells of the biliary tree. These cancers are typically classified by anatomic site of origin: intrahepatic cholangiocarcinoma (IHCC) and extrahepatic cholangiocarcinoma (EHCC), and gallbladder cancer (GBC). To date, complete surgical resection remains the mainstay of treatment especially for earlier stage disease. Unfortunately, most patients present with advanced or metastatic disease, when systemic chemotherapy is the only treatment option. Due to the paucity of effective treatments, BTCs have a dismal prognosis. There is a tremendous need to better understand the disease biology, discover new therapies, and improve clinical outcomes for this challenging disease. Next-generation sequencing has produced a more accurate and detailed picture of the molecular signatures in BTCs. The three BTC histologic subtypes are, in fact, quite molecularly distinct. IHCC commonly contain FGFR2 fusions and IDH 1 and 2 mutations, whereas EHCC and GBC tend to carry mutations in EGFR, HER2, and MAPK pathway. In light of this emerging knowledge, clinical trials have become more biomarker-driven, which allows capturing of subsets of patients that are most likely to respond to certain therapies. Many new and promising targeted therapeutics are currently in the pipeline. Here we review the genetic landscape of BTCs while focusing on new molecular targets and targeted therapeutics currently being investigated in biomarker-driven clinical trials.

Keywords: Biliary tract cancer (BTC); cholangiocarcinoma; gallbladder cancer (GBC); biologics

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Introduction

Biliary tract cancers (BTC) is a group of rare and aggressive malignancies arising from the epithelium of the biliary duct system. They are classified based on their anatomical site in the biliary tree [intrahepatic cholangiocarcinoma (IHCC) or extrahepatic cholangiocarcinoma (EHCC)] or gallbladder cancer (GBC) (Figure 1). IHCC is the most common BTC and the second most common hepatic malignancy, accounting for 10–20% of all primary hepatic malignancies (1,2). Owing to the insidious nature of this group of cancers, they are usually diagnosed at an advanced stage and carry a dismal prognosis. Surgery is potentially curative in early stage disease. In cases of advanced and metastatic disease, the current standard of care is systemic chemotherapy with gemcitabine and cisplatin. Clinical response rates to these cytotoxic chemotherapies are low, with a 5-year survival of less than 10% for all three BTC subtypes. In recent years, we have made strides in our understanding of the disease biology, as well as advancements in diagnostic techniques and novel therapeutic strategies. Notably, the genomic revolution has ushered in an era of high-throughput and deep molecular profiling, which has provided invaluable insight into actionable molecular alterations, as well as their prognostic significance. We have also developed
a greater appreciation for the molecular heterogeneity across the BTC subtypes, realizing that these anatomically classified subgroups exhibit distinct molecular architectures. Considering this emerging knowledge, clinical trial design has steered away from the “one-size-fits-all” mentality and has become more biomarker-driven. Currently there are several ongoing clinical studies investigating the efficacy of targeted therapies aimed at populations that underwent biomarker selection. In this review, we will highlight actionable molecular targets and their novel targeted therapeutics in current clinical trials.

**Epidemiology**

The incidence of BTC varies by geography and demographics, likely due to distinct environmental risk factors and genetic predisposition. Though BTcs are traditionally more common in Asian countries, their incidence has been rising in Western countries in recent decades (3). Though it is a rare disease, the global incidence is rising. Chronic inflammation and bile stasis in the biliary tract are thought to be major risk factors underlying the pathogenesis of these cancers. Specific risk factors include primary sclerosing cholangitis, liver fluke (Clonorchis, Opisthorchis) infection, hepatitis B and C infections, cholelithiasis or choledocholithiasis, cirrhosis, alcohol, smoking, and fatty liver disease (3,4).

**Current management**

Overall, the 5-year survival rate of BTcs is extremely low (10% for CAs and less than 5% for GBC) (5,6). Surgery is the only potentially curative modality but most patients are asymptomatic until late in the disease course and present with locally advanced or metastatic disease. Thus, only 10–15% of BTcs are amenable to surgery at initial presentation (7). Even though improved surgical techniques and better patient selection based on more advanced radiologic techniques have resulted in better tumor resection rates, the recurrence rates of these aggressive cancers remain high at 50–60% (7,8). The role of adjuvant therapy is poorly-defined and standard regimen is unclear due to the relative rarity of this disease which hinders large scale prospective studies (9,10). Therefore, the benefit of adjuvant treatment is commonly appraised from meta-analyses of multiple small retrospective studies that usually include more than one, if not all, subtypes of BTC. To more clearly determine the role of adjuvant treatment, two phase III randomized controlled trials are currently ongoing in the Europe to determine the role of adjuvant gemcitabine plus cisplatin (ACTICCA-1 trial, NCT02170090) or oxaliplatin (NCT01313377) versus observation for patients with resected BTC. Before results from these trials are available, current NCCN guidelines recommend adjuvant fluoropyrimidine or gemcitabine-based chemotherapy with consideration of radiation for patients with node-positive disease or R1/R2 resections.

For patients presenting with unresectable BTcs (locally advanced, recurrent, or metastatic), the current standard first-line therapy is a combination of gemcitabine and cisplatin. This regimen was established by the ABC-02 trial, the largest randomized phase III study to date, which showed a survival benefit of the combination as opposed to gemcitabine alone (11.7 vs. 9 months) (11). Other chemotherapy combinations (e.g., oxaliplatin, 5-FU, capecitabine, irinotecan) have demonstrated only marginal improvements in survival (12). Targeted therapies such as anti-EGFR or anti-VEGF antibodies have so far struggled to succeed in phase I or II clinical trials. Performing randomized control trials (RCT) for advanced BTcs has proven challenging due to the rarity of these malignancies, lack of effective agents, potential high heterogeneity within this diagnostic entity, and possibly fundamental differences among the three BTC subtypes (IHCC, EHCC, and GBC). In fact, next generation sequencing (NGS) and transcriptomic analyses have revealed that these BTC...
subtypes are molecularly distinct from one another, and therefore may respond differently to the same treatment strategy and should not be approached as a single entity for clinical trial design (13,14). To improve patient outcome, future clinical trial design must better stratify patients based on considerations of histologic and molecular subtypes, and allocate patients to the appropriate targeted agents driven by biomarkers that could predict treatment response.

**Genetic landscape**

Before the advent of NGS, our knowledge of genetic aberrations in BTCs was limited because older methodologies restricted mutational profiling to a few select oncogenes or hotspots (15). That technology previously allowed us to identify key signaling pathways altered in BTCs, such as the EGFR and vascular endothelial growth factor receptor (VEGFR) pathways. Thus, many of the first generation BTC trials targeted EGFR and VEGFR, but these targeted agents ultimately proved ineffective at improving clinical outcome (12). NGS, which allows for characterization of an entire genetic landscape through gene panels, whole exome, or transcriptome sequencing, has led to the discovery of many novel actionable mutations in BTCs (15). Thus, pre-clinical and clinical studies have expanded from targeting well-established pathways like EGFR and VEGFR to promising, novel alterations.

Recent studies employing NGS have shed light on distinctive molecular spectra across the BTC subtypes (13,14). FGFR2 gene fusions and mutations in IDH1/2 are predominantly observed in IHCC. KRAS and HER2 mutations are preferentially found in EHCC. Lastly, GBCs are enriched for mutations in EGFR, HER2, and PIK3CA. Figure 1 and Table 1 highlight these key genomic alterations along the biliary tract and gallbladder. Next, we will discuss key actionable aberrations in BTCs and the novel agents that target them in biomarker-driven clinical trials.

**Tyrosine kinase signaling**

*EGFR*

The EGFR family comprises four tyrosine kinase receptors (ERBB1–4) that regulate cell proliferation, survival, angiogenesis, and invasion through ligand binding and subsequent activation of signal transduction cascades involving the MAPK pathway (Ras-Raf-MEK-ERK) and the PI3K/AKT pathway (33) (Figure 2). Aberrant activation of the EGFR pathway is a common oncogenic event in BTCs and is associated with tumor recurrence and worsened outcome (16,18,26,34). Of the EGFR family members, *EGFR (ERBB1)* and *HER2 (ERBB2)* are most commonly altered in BTCs. Overexpression of EGFR occurs in 11–27% of IHCC, 5–19% of EHCC (26), and 12% in GBCs (35), whereas activating *EGFR* mutations are preferentially seen in GBC (4–18%), but rarely in CCAs (Table 1) (16,17).

<table>
<thead>
<tr>
<th>Variables</th>
<th>IHCC (%)</th>
<th>EHCC (%)</th>
<th>GBC (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tyrosine kinase signaling</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>EGFR</em></td>
<td>4</td>
<td>3</td>
<td>4–18</td>
<td>(16,17)</td>
</tr>
<tr>
<td><em>HER2</em></td>
<td>1.5–3</td>
<td>11–18</td>
<td>10–16</td>
<td>(16,18-20)</td>
</tr>
<tr>
<td><em>KRAS</em></td>
<td>17–30</td>
<td>12–40</td>
<td>0–13</td>
<td>(16,17,19-21)</td>
</tr>
<tr>
<td><em>BRAF</em></td>
<td>4–7</td>
<td>3</td>
<td>1–6</td>
<td>(16,19,22,23)</td>
</tr>
<tr>
<td><em>PIK3CA</em></td>
<td>5–6</td>
<td>7–9</td>
<td>8–14</td>
<td>(19,21,24,25)</td>
</tr>
<tr>
<td>FGFR2 fusions</td>
<td>6–50</td>
<td>0–5</td>
<td>0–3</td>
<td>(17,19,26-29)</td>
</tr>
<tr>
<td>IDH pathway</td>
<td>10–28</td>
<td>0–7</td>
<td>0</td>
<td>(19,21,27,30-32)</td>
</tr>
<tr>
<td><strong>Chromatin-remodeling genes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>ARID1A</em></td>
<td>17</td>
<td>12</td>
<td>13</td>
<td>(19,27)</td>
</tr>
<tr>
<td><em>BAP1</em></td>
<td>11</td>
<td>8</td>
<td>0</td>
<td>(17,27)</td>
</tr>
<tr>
<td><em>PBRM1</em></td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>(17,27)</td>
</tr>
</tbody>
</table>
Given that EGFR activation regulates several cellular functions important for carcinogenesis and is one of the most altered pathways in BTCs, there was strong rationale to evaluate it as a therapeutic target. However, extensive clinical testing with EGFR inhibitors has failed to show a survival benefit in advanced BTCs. Although earlier single arm phase II trials suggested possible benefits of EGFR antagonists cetuximab and panitumumab either as single agents or in combination with chemotherapy (36-39), larger RCTs of erlotinib, cetuximab or panitumumab in combination with gemcitabine plus oxaliplatin failed to show a progression-free survival (PFS) or overall survival (OS) benefit over chemotherapy alone in advanced BTCs (40,41). Of note, almost all of these trials have been performed without stratifying patients by molecular signatures that could predict response to anti-EGFR agents. In fact, none has used EGFR genomic alterations as a biomarker. Additionally, lessons from the colorectal cancer world have informed us that KRAS mutations negate response to anti-EGFR therapy (42-44). However, only a few of the BTC trials have used KRAS status to stratify patients. A recent phase II trial stratified BTC patients based on KRAS status, but failed to demonstrate that KRAS status predicted the population most likely to benefit from anti-EGFR therapy (45). Furthermore, two biomarker-driven trials that was restricted to KRAS wild-type patients failed to show a clinically significant improvement in PFS or OS using panitumumab combined with chemotherapy (46,47). These studies call into question the utility of KRAS status as a clinically relevant biomarker predictive of EGFR therapy response in BTC, as opposed to colon cancer. The relative importance of mutations in other EGFR pathway genes, such as BRAF, are being investigated as mechanisms of resistance to anti-EGFR agents (47,48).

HER2

HER2 overexpression and amplification are predominantly seen in EHCC and GBCs (10–18% for both) and rarely in IHCC (Table 1) (16,19,20,26,34,35). Like EGFR-directed agents, similarly disappointing results came out of trials with HER2 antagonists (including trastuzumab, lapatinib, afatinib) combined with chemotherapy in advanced BTC (49-51). Currently, there is an ongoing phase II trial with trastuzumab aimed at a selected group of HER2-positive BTC patients (Table 2).

VEGF

VEGF is the ligand that binds VEGFR, which initiates
signals to promote cancer growth and metastasis through stimulating angiogenesis. VEGF is overexpressed in BTCs and associated with enhanced metastasis, increased tumor recurrence, and worsened prognosis (34). Studies with antagonists of the VEGF pathway, including bevacizumab, cediranib, sorafenib have not yielded encouraging results (52-56).

**MAPK pathway**

Aberrations in cell-surface receptors and their ligands (e.g., EGFR, VEGF) can lead to constitutive activation of downstream cascades, including the MAPK arm (RAS-RAF-MEK-ERK, Figure 2). KRAS is a member of the RAS family and gain of function mutations in KRAS are one of the most common events in BTCs, with highest rates seen in EHCC, followed by IHCC, and lowest in GBC (16,17,19,20,57). KRAS is associated with lower median survival and perineural invasion (58). Its frequency also increases with disease stage (22). BRAF belongs to the RAF family of kinases that lie directly downstream of RAS (Figure 2). BRAF mutations are less frequent in BTCs (less than 10% across all subtypes) and are considered mutually exclusive with KRAS mutations (16,19,22,59). The most common BRAF mutation is V600E, but the mutational frequency is highly varied in BTCs ranging from 0–33% (60). The clinical significance of BRAF mutations is less well-established, with one study demonstrated an association with advanced tumor stage, higher likelihood of lymph node involvement, and worsened survival (22).

Targeting the MAPK pathway has remained a challenge. Recently, the phase I ABC-04 study of selumetinib, a MEK inhibitor, in combination with gemcitabine and cisplatin failed to show clinical benefit in in advanced or metastatic BTC (61). Even attempts to block multiple components of the MAPK pathway using multikinase inhibitors like sorafenib have not proved fruitful (62-65). These disappointing results are in stark contrast to melanomas, which frequently harbor the BRAF V600 mutations, where use of the BRAF inhibitors vemurafenib or dabrafenib has achieved a striking survival benefit (66-68). Recently, dual inhibition of BRAF with vemurafenib or dabrafenib and MEK with trametinib in BRAF V600-mutated melanoma patients has led to further survival improvements (69-71). Currently, there is an ongoing phase II trial with dabrafenib combined with trametinib for BRAF V600-mutated rare cancers including BTCs (Table 2).

Multiple signaling pathways seem to be involved in the pathogenesis of BTCs, rendering the decision of which pathways to target challenging. Moreover, no oncogene addiction pathway has been pinpointed. Targeting single pathways either as monotherapy or in combination with
chemotherapy has shown varying degrees of improvements in response rates, but these have not translated to clinically significant increases in PFS or OS. Currently, some clinical trials are using a multi-target approach by using multikinase inhibitors or a combinatorial approach with multiple agents aimed at different pathways (12,72). Results from studies using multikinase inhibitors regorafenib and pazopanib are anxiously awaited.

**Novel targets**

Over the recent years, genomic profiling using NGS has revealed the presence of novel alterations in BTCs such as recurrent fusion events (FGFR2 and ROS1 fusions), somatic mutations in metabolic enzymes (IDH1 and 2) (17-19,21,23,26-31,57,73,74), and chromatin-remodeling genes (ARID1A, BAP1, PBRM1) (17,19,27).

**FGFR2 fusions**

FGFR2 is a member of the fibroblast growth factor family of receptor tyrosine kinases that regulate cell proliferation, differentiation, apoptosis (75). Alterations in this pathway through activating mutations, amplifications, or chromosomal translocation have been implicated in malignant transformation (76). Chromosomal fusions occur between exons 1–19 of FGFR2 and various genomic partners (e.g., AHCYL1, BICC1, PARK2, KCTD1, MGEA5, TACC3, TXLNA) in BTCs (17,19,26–29). The resulting fusion protein undergoes ligand-independent dimerization and subsequent autophosphorylation, which leads to constitutive activation of downstream signaling pathways, such as MAPK (76) (Figure 2). The oncogenic potential of FGFR2 fusions has been demonstrated in vitro (23,28,77,78) and in vivo (28). Screening for fusions by massive parallel sequencing or FISH-based assays has revealed a wide range of IHCC (6–50%) containing FGFR2 fusions, whereas EHCC and GBC rarely do (Table 1).

In preclinical studies, the presence of FGFR2 fusions seems to predict high sensitivity to FGFR2 inhibitors (23,28,73,77,78). This provided the catalyst to target the FGFR pathway specifically in tumors harboring these fusions. FGF pathway antagonists include small molecule tyrosine kinase inhibitors that act at the receptor level to suppress oncogenic signaling (28). Clinical efficacy of FGFR2 inhibitors is being investigated in biomarker-driven clinical trials aimed at patients harboring FGFR2 pathway alterations (Table 2). The pan-FGFR inhibitor BGJ398 has potent activity against FGFR1–3 and is under evaluation in advanced CCAs with FGFR genetic alterations in two phase II studies (Table 2). Preliminary results from one of the studies (NCT02150967) was recently reported. Amongst the 26 patients with advanced or metastatic CCA harboring FGFR2 fusions or other alterations, the disease control rate was 82% (79). The drug was well tolerated except for hyperphosphatemia.

Pontatinib is an example of a non-selective pan-FGFR inhibitor that is far along in clinical development. In a preclinical study, treatment with pontatinib resulted in biochemical CA 19-9 response with tumor shrinkage in a patient with the FGFR-MGEA5 fusion (73). Another patient in the study with FGFR-TACC31 fusion whose disease had progressed on pazopanib (another non-selective FGFR inhibitor) was treated with pontatinib therapy, resulting in stabilization of disease (73). This preliminary evidence supported assessing the anti-tumor activity of pontatinib in clinical trials. Pontatinib is being investigated in a phase II trial of advanced BTCs harboring FGFR2 gene fusions detected by either NGS or FISH (NCT02265341, Table 2). Another ongoing phase II trial is assessing the efficacy of pontatinib in advanced malignancies including CCA with any FGFR aberrations (mutations, fusions, amplifications) (NCT02272998, Table 2). Other ongoing phase II studies include oral pan-FGFR selective small molecular inhibitors INCB054828, erdafitinib (JNJ-42756493), ARQ087 (Table 2). Preclinical and phase I studies have suggested that these compounds have potent and selective anti-tumor activity against FGFR-mutated cancers (80-83). A recently developed monoclonal antibody against FGFR2 (BAY1179470) showed tumor suppressive potential in tumors with high FGFR2 expression (84). Phase I testing of this antibody just recently completed (NCT01881217). Another phase I trial with oral pan-FGFR inhibitor AZD4547 also just completed (NCT00979134).

**IDH1/2**

*IDH1* and *IDH2* encode metabolic enzymes that participate in the Krebs cycle. Mutations in *IDH1* and *IDH2* result in the accumulation of the oncometabolite 2-hydroxyglutarate, which affects cell differentiation, survival, as well as DNA methylation. The epigenetic alterations caused by mutations in *IDH1/2* lead to a blockade of hepatocyte differentiation, causing an increase in hepatic progenitor cells, which eventually results in tumorigenesis (85). *IDH* mutations...
have been seen in solid tumors, including gliomas, and recently identified in BTCs. They occur primarily in IHCC (10–28%) and rarely in EHCC and GBCs (19,21,27,30,31) (Table 1). The most common $IDH1$ and $IDH2$ mutations cluster at the hotspot codons 132 and 172, respectively (86). The prognostic significance of these mutations remains to be fully elucidated, as there is some conflicting data. Two studies have correlated $IDH$ mutations with decreased survival in IHCC compared to wild-type cases (27,31). Another study failed to demonstrate an association between $IDH$ mutation status and survival (32). In contrast, a large cohort of IHCC samples (n=326) showed $IDH$ mutations were associated with longer time to recurrence (30).

The efficacy of pharmacologically targeting the mutant $IDH$ enzymes has been demonstrated in other types of tumors. $IDH1$ inhibitor AGI-5198 slowed the growth of $IDH$-mutant glioma cells (87) and $IDH2$ inhibitor AGI-6780 selectively inhibited the growth of leukemic cells carrying mutant $IDH2/R140Q$ (30). The role of IDH inhibitors in IHCC is currently being investigated. AG-120, an IDH1 inhibitor, has been shown to transiently stabilize disease progression in patients with $IDH1$-mutant IHCC. The expansion phase is currently underway (NCT02073994, Table 2). AG-120 is also being tested in the ongoing phase III RCT “ClariDH” in patients with advanced or metastatic CCA carrying an $IDH1$ mutation (Table 2). A phase I/II trial with AG-221 (IDH2 inhibitor) has just completed. A recent study showed that a subset of IHCC tumors with $IDH$ mutations are exquisitely sensitive to the multikinase inhibitor dasatinib (88). This evidence paved the way for designing a phase II trial using dasatinib in IHCC cases harboring mutations in $IDH1$ or 2 (Table 2). Other agents that have demonstrated preclinical efficacy and are now in phase I testing include BAY1436032 (IDH1 inhibitor), IDH305 (IDH1 inhibitor), and AG-881 (IDH1/2 inhibitor) (89).

$ROS1$

$ROS1$ kinase fusions between kinase domain of $ROS$ and $FIG$ have been found in 8.7% of CCAs (74). The resultant $FIG$-$ROS1$ fusion protein has oncogenic potential in vitro and in vivo and can be inhibited by pharmacological targeting (74,90). A phase II trial of crizotinib (ALK/$ROS1$ inhibitor) in patients with $ALK$, $MET$, or $ROS1$ alterations is underway (Table 2). LDK378, a $ALK/ROS1$ inhibitor, is being investigated in $ROS1$-overexpressing advanced CCAs (Table 2). Entrectinib, another $ALK/ROS1$ inhibitor, is being tested in CCAs carrying $ROS1$ gene fusions.

Conclusions

BTCs are highly aggressive tumors that carry a dismal prognosis. Historically, the BTC subtypes have been studied as a single entity. Application of NGS technologies has allowed for enhanced characterization of the distinct genetic landscapes in the various BTC subtypes. FGF and $IDH$ pathway alterations are commonly seen in IHCC, whereas alterations in the $EGFR$-$MAPK$-$PI3K$ pathway occur more frequently in EHCC and GBC. The molecular heterogeneity across these subtypes likely confers differential responses to various treatments. Thus, therapy should be customized based on mutational spectra. To optimize clinical trial design, targeted therapies should be matched to specific molecular alterations through patient biomarker selection. Past investigations into agents targeting receptor tyrosine kinase and $MAPK$ pathways have not shown significant benefit over standard chemotherapy regimen. However, improvements in genetic profiling have unveiled novel actionable mutations, such as FGFR2 fusion proteins and mutated $IDH1/2$. Agents targeted against these newly discovered aberrations are being actively investigated in clinical trials and hold the promise of improving clinical outcomes in this devastating orphan disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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