Review Article



# New frontiers in the treatment of cholangiocarcinoma: a narrative review

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**Objective:** This is a narrative review of the standard chemotherapy treatments for unresectable cholangiocarcinoma and the evolution to more targeted therapies.

**Background:** Cholangiocarcinoma only represents a small percentage of newly diagnosed malignancies in the United States; however, mortality rates are high. Surgical resection remains the only curative approach to this disease with chemotherapy as the main treatment for advanced disease. Gemcitabine and cisplatin chemotherapy is the gold standard for first line treatment based upon the ABC-02 clinical trial with overall survival being less than 1 year but we are making progress with novel therapies. Genomic analysis of tumors has become standard of care for many malignancies and matched therapy is improving survival.

**Methods:** Literature search was performed through Medline and PubMed to identify pivotal biliary cancer clinical trials. Authoritative texts were utilized and focused on targets with approved therapies or therapies undergoing review with the FDA

**Conclusions:** Genomic sequencing of biliary cancers has changed the landscape of treatment as we divide biliary cancers into molecular subtypes. MSI high was the first tumor agnostic biomarker to be approved for the use of checkpoint inhibitors. TRK inhibitors were approved for tumors with TRK fusions; however, this is a small population of cholangiocarcinoma. Pemigatinib is the first therapy to be approved for FGFR2 fusions in intrahepatic cholangiocarcinoma occurring in 10–15% of patients. IDH1 mutations occur in 20–30% of intrahepatic cholangiocarcinoma and ivosidenib is undergoing review with the FDA. As new therapies are approved for the treatment of cholangiocarcinoma, more treatment options will improve the survival of this deadly disease.

**Keywords:** Chemotherapy; cholangiocarcinoma; biliary cancer

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## Introduction

Cholangiocarcinoma consists of a diverse group of malignancies throughout the biliary system ranging from gallbladder to intrahepatic biliary and extrahepatic biliary cancer. This is a rare cancer comprising only 2.4% of all new cancers diagnosed in United States. It is estimated that about 42,000 new cases are diagnosed yearly with about 30,000 deaths (1). This high mortality rate reflects the aggressive nature of the disease. Patients with early stage cancer commonly are asymptomatic and only present after

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the disease becomes more advanced causing complications such as jaundice or pain. Imaging is a critical aspect of determining resectability for localized disease. A contrast enhanced computed tomography or magnetic resonance cholangiopancreatography allows for more accurate staging to evaluate invasion into the portal vein or main hepatic artery. This also allows for evaluation of invasion into adjacent organs which may make the tumor unresectable. Lymph node involvement is also visualized to rule out distant spread outside the confines of standard resection. But even for localized disease, 5-year survival rate after resection for patients with lymph node positive disease has been reported around 10% indicating early microscopic spread of disease. Thus, there has been much effort to develop novel therapies.

Cholangiocarcinoma can be subdivided into 3 groups. Perihilar cholangiocarcinoma comprises the largest percentage of biliary cancers with about 50% to 60% originating in this region. The second most common site of biliary cancers is in the distal extrahepatic bile ducts comprising about 20% to 30% of cholangiocarcinomas. The remainder arise in the intrahepatic bile ducts and only represent 10% to 20% of all cholangiocarcinomas. The subtype of cholangiocarcinoma impacts the patterns of recurrence after surgery with perihilar tumors having a higher local relapse rate. Gallbladder cancer however has a much higher propensity for distant metastatic spread with some studies reporting an incidence as high as 85% (2). We are also now learning the biology of cholangiocarcinoma differs by the subtype and response to chemotherapy varies with the location of the tumor. We have seen through genomic analysis molecular alterations that can be targeted with small molecules which occurs more frequently in intrahepatic cholangiocarcinoma. This article provides an overview of our treatment options for cholangiocarcinoma and the progress toward personalized medicine for this deadly disease. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/dmr-21-38).

## Objectives

(I) Review the standard cytotoxic chemotherapy for the management of unresectable cholangiocarcinoma.
(II) Review important targets in biliary cancers with approved therapies.
(III) Identify challenges with immunotherapy and future directions.
(IV) To provide the reader with an overview of the treatment options for cholangiocarcinoma.

## Methods

MEDLINEPlus is the premier database of the National Library of Medicine containing more than 27 million references to journal articles published from 1966 to present. Citations are regularly added to PubMed allowing easy access to key articles in the field. Utilizing search terms of biliary cancer, cholangiocarcinoma, gallbladder cancer, genomics, mutations and targeted therapy yielded over 2,000 results. Authoritative texts were utilized to identify key articles for this review. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Evolution of cytotoxic chemotherapy

In 1996, Glimelius and colleagues published results of their randomized clinical trial in patients with pancreatic or biliary cancer. 90 patients received either 5-fluorouracil (5FU) with leucovorin and etoposide versus best supportive care. Results showed a significant improvement in median overall survival of 6 versus 2.5 months (P<0.01) with 5FU chemotherapy. Quality of life was also improved (3). Pooled analysis of 104 trials showed response rates and tumor control were higher for the subgroup receiving a combination gemcitabine or 5FU based chemotherapy illustrating the efficacy in controlling cancer. Another retrospective study of 304 patients with unresectable biliary tract cancers showed treatment with gemcitabine alone, a cisplatin-based regimen, or a fluoropyrimidine-based regimen improved survival with patients receiving gemcitabine having a lower risk of death. Based upon these results, gemcitabine was the backbone for future trials.

The pivotal phase III ABC-02 study defined the standard of care treatment for over a decade. This trial randomized 410 patients with cholangiocarcinoma, gallbladder cancer, or ampullary cancer to either gemcitabine and cisplatin or gemcitabine chemotherapy alone. The gemcitabine and cisplatin chemotherapy were given at a dose of 1,000 and 25 mg/m$^2$, respectively on a day 1 and 8 schedule every 21 days. The combination improved OS and PFS by 30% over gemcitabine. Median OS was 11.7 months and 8.1 months (HR, 0.64; 95% CI, 0.52–0.80; P<0.001), and median PFS was 8.0 *vs.* 5.0 months (HR, 0.63; 95% CI,

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0.51–0.77; P<0.001), both in favor of the combination arm. The treatment was well tolerated with the combination arm having a higher rate of neutropenia without a significant increase in infections. Gemcitabine and cisplatin chemotherapy proved to be the reference standard first line treatment for advanced unresectable biliary cancers; however, there have not been many phase 3 clinical trials comparing combination chemotherapy in this disease (4).

In many parts of the world, gemcitabine and oxaliplatin chemotherapy has been used as the standard treatment for advanced biliary cancer. Several phase 2 trials have shown response rates ranging from 26–41% likely from selection bias of patients on smaller studies (5-7). The median overall survival ranged from 8.8 months to 15.4 months. Typically, the response rates and median overall survivals decrease in the larger phase 3 trials; however, no comparative trial has been completed. Ease of administration may have factored into the use of gemcitabine and oxaliplatin with no hydration requirements to prevent nephrotoxicity thus decreasing infusion times. A phase 3 noninferiority trial was conducted in patients with metastatic biliary tract cancers comparing gemcitabine and oxaliplatin chemotherapy versus XELOX. Gemcitabine was given at a dose of 1,000 mg/m$^2$ on days 1 and 8 and oxaliplatin at 100 mg/m$^2$ on day 1 every 3 weeks. Capecitabine was given at a dose of 1,000 mg/m$^2$ twice per day on days 1 through 14 and oxaliplatin 130 mg/m$^2$ day 1 every 3 weeks. The primary endpoint of the study was noninferiority of 6-month progression free survival between the 2 arms. Results showed the 6-month progression free survival rate was 5.3 months for the GEMOX group versus 5.8 months for the XELOX group and there was no difference in the median overall survival. The overall response rate was 24.6% for GEMOX and 15.7% for XELOX (8).

As seen with other malignancies, dose intensity of chemotherapy impacts response rates and overall survival. Gemcitabine and nab-paclitaxel in a phase 2 trial showed an objective response rate of 30% with a median overall survival of 12.4 months. The toxicity profile was manageable since this regimen is also utilizing pancreatic cancer. Grade 3 and 4 neutropenia occurred in 43% of patients (9). The addition of cisplatin chemotherapy to gemcitabine and nab-paclitaxel showed encouraging results in a phase 2 clinical trial. The response rate increased to 45% with a median overall survival of 19.2 months. There were more toxicities associated with this triple combination and grade 3 or higher adverse events occurred in 58% of patients (10). Based upon the results of the phase 2 clinical trial, a phase 3 clinical trial was conducted in SWOG. S1815 is a randomized phase 3 clinical trial evaluating gemcitabine, cisplatin and nab-paclitaxel versus gemcitabine and cisplatin and newly diagnosed advanced biliary tract cancers. Accrual on this trial was rapid and completed accrual February 15, 2021. Results will be presented in 2022.

There has been limited studies defining second line treatment for advanced biliary cancer. The regimen utilized depends upon the first line of chemotherapy. ABC–06 was a randomized phase 3 study evaluating modified FOLFOX chemotherapy compared to active symptom control after prior gemcitabine and cisplatin chemotherapy. This showed that additional systemic chemotherapy improved survival compared to best supportive care. For patients that initiate first-line treatment with GEMOX, 5-FU based chemotherapy becomes the standard treatment. This is based upon small phase 2 clinical trials and should only be given if molecular alterations or not found in the tumor DNA. The sequencing of the tumor DNA has transformed the management of solid tumors.

## Genomic analysis of cholangiocarcinoma

The three-dimensional structure of DNA was discovered by Watson and Crick in the 1950s which laid the ground work for future discoveries. It was not until the 1970s that the Sanger method of DNA sequencing technology permitted the decoding of DNA. As next generation sequencing evolved over time, the costs significantly decreased and allowed for the genomic analysis of tumors. This gave us a much better understanding of the molecular pathways driving tumor growth. As we have seen in non-small cell lung cancer, targeted therapy changed the landscape of the management of this disease. Sequencing of cholangiocarcinoma has identified molecular subtypes that are targetable (11). In the Molecular Screening for Cancer Treatment Optimization (MOSCATO)-01 trial, 34 subjects underwent molecular screening with 23 finding alterations. Of the 23 subjects, 18 received targeted therapy with a 33% objective response rate. The median progression free survival was 5.2 months (12). Several on-going trials in the United States including the NCI MATCH and TAPUR are providing access to targeted therapies for specific molecular alterations.

## FGFR mutations

The FGFR family of receptors is composed of FGFR 1–5 that are implicated in cell proliferation, differentiation,

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angiogenesis and intracellular survival. FGFR 1–4 consist of an intracellular tyrosine kinase domain involved in signaling. FGFR alterations have been observed in several different malignancies including endometrial cancer, breast cancer, ovarian cancer, urothelial cancer and brain cancer. In cholangiocarcinoma, FGFR 2 gene alteration is involved in the pathogenesis of cancer. This is nearly exclusively found in intrahepatic cholangiocarcinoma and not perihilar or extrahepatic cholangiocarcinoma with the fusion being detected in about 10% to 15% of patients. These tend to occur more frequently in younger patients and are associated with more indolent disease progression. Fusions that involve other members of the FGFR family are rare in biliary tract cancers, with an incidence below 0.5%.

Numerous small molecule inhibitors have been developed over the last decade. These nonselective tyrosine kinase inhibitors hit various targets including FGFR. Agents such as lenvatinib, pazopanib and regorafenib have been approved for various malignancies; however, in cholangiocarcinoma there has been limited activity seen. Targeting angiogenesis was the main mechanism of action for these agents with limited activity on FGFR signaling. The next generation of FGFR small molecule inhibitors were more selective. Infigratinib (BJG 398) selectively inhibits FGFR 1–3 in nanomolar concentrations. When tested in cholangiocarcinoma patients with FGFR2 fusions, the median progression free survival was 5.8 months with an overall response rate of 18.8% (13). With a more potent irreversible FGFR inhibitor futibatinib (TAS-120) encouraging results were seen in the FOENIX-CCA2 phase II trial. Sixty-seven intrahepatic cholangiocarcinoma patients harboring FGFR2 gene fusions were treated with futibatinib. The results were impressive with an overall response rate of 34.3% and activity was seen in patients that received prior FGFR inhibitors. Thus, an irreversible inhibitor could reverse resistance.

Pemigatinib was the first small molecule inhibitor targeting FGFR 1–3 approved for the treatment of intrahepatic cholangiocarcinoma harboring FGFR2 fusions. The FIGHT-202 trial was an open label phase 2 single arm study studying pemigatinib in patients with cholangiocarcinoma and FGFR 2 fusions or alterations. Pemigatinib is orally administered for 14 out of 21 days. 107 patients were accrued and 35.5% of the patients harboring FGFR2 fusions or alterations had an objective response. 3 patients achieved a complete response and the median progression free survival was 6.9 months and the median overall survival was 21.1 months. The treatment was tolerable with hyperphosphatemia being the most frequent reported adverse event. This was observed and over 60% of the subjects. Hypophosphatemia was only observed in 12% of patients. Arthralgias and abdominal pain were observed in less than 10% of patients. There was no treatment related death seen on study. Based upon these results, the FDA granted accelerated approval of pemigatinib on April 17, 2020 for patients with metastatic cholangiocarcinoma harboring FGFR2 fusion or alteration detected by Foundation One CDX (14).

## Isocitrate dehydrogenase (IDH) mutations

IDH is an essential metabolic enzyme of the Krebs cycle. There are 2 main subtypes IDH1 localized in peroxisomes and IDH2 localized in mitochondria. Mutations in IDH leads to gain of function of the enzyme leading to increased D-2-hydroxyglutarate, an oncometabolite. This activates DNA methylation resulting in epigenetic dysfunction and upregulation of the VEGF pathway promoting tumorogenesis. Mutations in this pathway have been found in various malignancies including cholangiocarcinoma, chondrosarcoma, thyroid carcinoma, glioma and acute myeloid leukemia.

IDH 1 mutations were found in about 25% of cholangiocarcinomas with only about 3% having IDH 2 mutations. They are most frequently seen in intrahepatic cholangiocarcinoma. With specific inhibitors for IDH1 being available, this led to biomarker driven trials. The phase 3 ClarIDHy trial enrolled 187 patients with previously treated cholangiocarcinoma and IDH1 mutation to either ivosidenib at 500 mg daily or placebo. Results were presented at the 2021 ASCO GI symposium which showed an improvement in median progression free survival (2.7 versus 1.4 months; $P<0.0001$) and a trend toward better overall survival. The study included a crossover from placebo to active treatment which likely impacted the overall survival. Results from this trial continue to support molecularly driven therapy however the small improvement in median progression free survival in addition to the high cost of therapy may limit its use (15). Ivosidenib is currently under review with the FDA.

## NTRK fusions

NTRK1 was identified as oncogene in 1982 by Mariano Barbacid and colleagues studying a human tumor colon cancer specimen. This proto-oncogene produced TRKA protein which is expressed in the nervous system and

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is stimulated by nerve growth factor. NRTK 2 and 3 encode for TRK B and C. Genomic translocations lead to constitutive activation of receptor tyrosine kinases leading to cellular proliferation. This alteration is rare in cholangiocarcinoma with only about 1–3% of cholangiocarcinoma having this alteration. There are 2 drugs approved by the FDA for the treatment of patients with an TRK gene fusion. Larotrectinib was approved in 2018 and entrectinib in 2019. Larotrectinib is a selective inhibitor of TRK A, B and C (16). Entrectinib targets TRK A, B and C in addition to ROS1 and ALK (17,18).

## Immunotherapy for cholangiocarcinoma

Immune checkpoint inhibitors have been shown to be beneficial in patients with defects in the DNA damage repair system. Patients with MSI high tumors or high tumor mutation burden have shown durable treatment responses. In the phase 2 keynote-158 study 22 patients with cholangiocarcinoma were treated with pembrolizumab. There were 9 objective responses with 2 complete responses and a medium duration a response of up to 25 months. The incidence of MSI high cholangiocarcinoma is only 3% (19). Tumor mutation burden is another predictor of response to immunotherapy and has been found in about 3 to 4% of biliary cancers. However, the mutations/Mb across the various next generation sequencing platforms can vary and impacts response to immunotherapy. For the Foundation One CDx assay, TMB >10 mut/Mb is considered high and pembrolizumab is approved for tumors testing positive with this assay (20). However, with other platforms, the cutoff of 10 may not be high and predictive of response. Further studies are needed to evaluate responses to checkpoint inhibitors to define to proper cutoff point for TMB with the various sequencing platforms (21).

Single agent activity with checkpoint inhibitors has been low in a non-selected patient population. In the second and third line setting, the objective response rate seen with single agent pembrolizumab was 10% and 12.5% respectively (20). In a phase 2 trial with nivolumab the investigator assessed objective response rate was 22%; however, by central independent review it was only 11% (22). The combination of nivolumab and ipilimumab has shown superior efficacy in various solid tumors. The combination was tested in biliary cancer. Nivolumab was given at a dose of 3 mg/kg and ipilimumab at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks for up to 96 weeks. 39 patients with biliary cancer were enrolled and the objective response rate observed was 23%. None of the patients had microsatellite unstable tumor and the responses observed were in the intrahepatic cholangiocarcinoma as well as gallbladder cancer. The median progression free survival was 2.9 months with a median overall survival of 5.7 months. This was in a patient population that it failed at least 1 line of therapy (23).

## Discussion

Biliary cancers consist of gallbladder cancer, intrahepatic, perihilar, extrahepatic and ampullary tumors with the pattern of spread as well as the response to systemic therapy varying depending upon the location. This overview provides the reader with a foundation of the current standard treatment options but is not meant to be a definitive comprehensive review. The field is rapidly evolving and genomic analysis of biliary cancers has opened the door for more targeted therapies. Our review covers the targeted therapies that have been approved but many targets are under investigation as we learn about the driving mechanisms of tumor cell proliferation. For example, glutamate dehydrogenase is an important component of glutamine metabolism that provide energy for tumor growth. Signaling through the TGF-B pathway has been implicated in tumorigenesis. Inhibitors of this pathway are in development which may play a role in the treatment of this disease. Another area of interest involves the epigenetics of cancers. In cholangiocarcinoma, oncometabolites can lead to epigenetic aberration with DNA hypermethylation affecting gene expression leading to tumorigenesis. Histone deacetylase inhibitors and DNA methyl transferase inhibitors are undergoing investigation but thus far has not shown significant activity in cholangiocarcinomas. Finally, targeting defects in DNA damage repair genes. with PARP inhibitors have been proven effective for various malignancies and the same will likely hold true for biliary cancers.

Over the last decade, immunotherapy has changed cancer care for many patients improving survival with minimal toxicities as compared to cytotoxic chemotherapy. For biliary cancers, checkpoint inhibitors alone have not had the same success. Immunotherapy combinations are now being explored and have shown promise improving the potential for the immune system to recognize the cancer. NCT03311789 was a phase 2 clinical trial evaluating the combination of gemcitabine and cisplatin chemotherapy with nivolumab in cholangiocarcinoma patients. This was a small study of only 27 patients however the investigators

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reported an overall response rate of 55.6% with 5 complete responses. This suggests a potential synergistic effect combining immunotherapy with chemotherapy however this needs to be studied further in a larger clinical trial. Additional studies are being conducted evaluating targeted therapy in combination with immunotherapy and is another potential promising avenue.

Patients with unresectable disease have incurable cancer and the optimal sequencing of therapy is critical for prolonging life. This is achieved by minimizing the toxicities of our therapies to achieve a higher therapeutic index and allowing patients to remain on treatment for a longer period of time (3). We have seen with our targeted therapies an improvement in progression free survival thus allowing patients to have multiple lines of treatment. However, these molecular alterations are rare and more commonly seen in intrahepatic cholangiocarcinoma which is a smaller percentage of biliary cancers. Additional research is needed to better understand molecular pathways that are driving growth to improve the development of novel therapeutics.

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