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Cholangiocarcinoma: An Emerging Target for Molecular Therapy

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Key Messages

- Cholangiocarcinoma has been traditionally considered a tumor with poor prognosis.
- Only 35% of patients are candidates for surgical treatment, of which another 35% subsequently relapse within 2 years.
- Overall survival of metastatic cholangiocarcinoma patients is <1 year.
- Novel therapies with fibroblast growth factor receptor, isocitrate dehydrogenase, and checkpoint inhibitors gave new hope in treatment of advanced tumors.

Keywords
Cholangiocarcinoma · Metastatic disease · Fibroblast growth factor receptors 2 · Isocitrate dehydrogenase · Targeted therapy · Immunotherapy

Abstract
Background: Cholangiocarcinoma has been traditionally considered a tumor with poor prognosis. Until now, surgical treatment has been the only more or less effective approach.
Summary: Over 10 years, chemotherapy with a combination of gemcitabine and cisplatin remains the standard first-line therapy for patients with locally advanced or metastatic cholangiocarcinoma, which leads to a median overall survival of 11.7 months. Several inhibitors of HER (ERBB), HGF/c-MET, Hedgehog, KRAS-BRAF-MEK-ERK, and PI3K/AKT/mTOR signaling pathways did not show their superiority to standard chemotherapy. The rise of hope is associated with the emergence of novel fibroblast growth factor receptors and isocitrate dehydrogenase inhibitors as well as immune checkpoint inhibitors.

Introduction

Biliary tract cancers constitute a group of tumors arising from the epithelium of intra- and extrahepatic bile ducts (cholangiocarcinoma) and the gallbladder [1]. The term "cholangiocarcinoma" comprises 3 types of tumors with different risk factors, characteristics, and treatment approaches: these are intra- and extrahepatic tumors and malignancies involving the bile ducts of the hilar bifurcation, belonging to extrahepatic tumors (Klatskin tumor). Biliary tract cancers are thought to account for about 3% of all gastrointestinal cancers; intrahepatic cholangiocarcinomas account for about 10% of cases of primary liver cancers. Among cholangiocarcinomas, Klatskin tumor accounts for 50% of cases, of which 40% are distal tumors and 10% are intrahepatic tumors [1]. The average incidence of cholangiocarcinoma in the United States is 1.26 cases per 100,000 population [1, 2].

Cholangiocarcinoma has been traditionally considered a tumor with poor prognosis. Until now, surgical treatment has been the only more or less effective approach. However, even it is a viable treatment option for

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Table 1. Results of trials in patients with metastatic cholangiocarcinoma

Study/result	Objective response rate, %	Progression-free survival, months	Overall survival, months
MET inhibition			
Phase 2 study, cabozantinib [12]	0	1.8	5.2
FGFR inhibition			
Phase 2 study (FIGHT-202), pemigatinib [19]	35.5	6.9	21.1
Phase 2 study, infigratinib [21]	26.9	6.8	12.5
IDH1 inhibition			
Phase 3 study (ClarIDHy), ivosidenib [25, 26]	2	2.7	10.3
Phase 1 study, ivosidenib [27]	5	3.8	–
Immune checkpoint inhibitors			
Phase 1 study, nivolumab with gemcitabine and cisplatin[1] [30]	37	4.2	15.4
Phase 2 study, nivolumab [31]	22	3.68	14.24
Phase 1b study (KEYNOTE 028), pembrolizumab [32]	13	1.8	6.2
Phase 2 study (KEYNOTE 158), pembrolizumab [32]	5.8	2	7.4
Phase 1 study [33]			
Durvalumab alone	4.8	–	8.1
Durvalumab/tremelimumab	11		10.1
Phase 2 randomized study [34]			
Atezolizumab alone	32.3	1.87	Not mature
Atezolizumab/cobimetinib	45.1	3.65	

FGFR, fibroblast growth factor receptor; IDH, isocitrate dehydrogenase. [1] This combination was studied in treatment-naive patients.

only 35% of patients [3], of which another 35% subsequently relapse within 2 years [4]. Over 10 years, chemotherapy with a combination of gemcitabine and cisplatin remains the standard first-line therapy for patients with locally advanced or metastatic cholangiocarcinoma, which leads to a median overall survival of 11.7 months [5]. Previously, upon disease progression on first-line chemotherapy, patients were left without effective treatment options. Attempts to use different chemotherapy regimens, both single-agent chemotherapy and combinations, have failed [6–8]. Fluoropyrimidines and their combinations with oxaliplatin or irinotecan are empirically prescribed as subsequent-line therapy in order not to leave the patient untreated [1].

In the era of targeted therapy, researchers tried to use the HER (ERBB), Hedgehog, KRAS-BRAF-MEK-ERK, and PI3K/AKT/mTOR signaling pathway inhibitors, which have proven effective in other tumors, in the treatment of biliary tract cancer; however, no study showed their superiority to standard chemotherapy [9]. Certain hopes were also associated with the inhibition of MET signaling, which is often activated in cholangiocarcinoma and promotes carcinogenesis by increasing angiogenesis and invasion. MET is overexpressed in 20–68% of cholangiocarcinomas [10, 11]. In the phase 2 study, previously treated patients with inoperable or metastatic cholangiocarcinoma received cabozantinib, a potent VEGFR and MET inhibitor [12]. Unfortunately, cabozantinib demonstrated limited activity and significant toxicity. The median progression-free survival was only 1.8 months and the median overall survival did not exceed 6 months. Again, targeted therapy has failed. Most recently, scientists have turned their attention to new molecular alterations in cholangiocarcinoma cells, namely, in the family of fibroblast growth factor and fibroblast growth factor receptors (FGFRs), as well as in isocitrate dehydrogenase (IDH) 1 and 2 (Table 1). Moreover, immunotherapy that has shown promising results in other tumors has turned to cholangiocarcinoma (Table 1).

FGFR Inhibition

FGFR alterations occur on average in 7.1% of all cancer patients [13] and are the potential therapeutic targets in some gastrointestinal tumors, for example, gastric cancer [14, 15]. Cholangiocarcinoma is a tumor with the most common FGFR alterations. Thus, rearrangements

and fusions in the FGFR genes, in particular, *FGFR2*, were detected in 6.1–16% of patients [13, 16, 17]. Therefore, it was logical to develop and study FGFR2 inhibitors in these patients.

On April 17, 2020, the US Food and Drug Administration (FDA) approved under accelerated process the first FGFR1-3 inhibitor, pemigatinib, for the treatment of patients with metastatic cholangiocarcinoma harboring *FGFR2* gene fusions or rearrangements, previously treated with standard chemotherapy [18]. The FDA's decision was based on the results of a multicenter, open-label, phase 2 trial FIGHT-202 [19]. This study screened 1,206 patients, of which 107 patients had *FGFR2* gene fusions or rearrangements, as detected using the FoundationOne CDx test. Pemigatinib was used at a dose of 13.5 mg orally, daily for a 21-day cycle (2 weeks on, 1 week off). The primary endpoint was the objective response rate in patients with FGFR2 alterations.

With a median follow-up of 17.8 months, the objective responses were reported in 38 patients, which amounted to 35.5%. Three patients achieved complete response to treatment. This was in line with the statistical hypothesis and the study reached its primary endpoint. The response developed quite quickly, at 2.7 months, and was prolonged (taking into account the patient cohort and the type of tumor) – lasted for 7.5 months. The median progression-free survival was 6.9 months. The median overall survival with continued follow-up was calculated as 21.1 months. Hyperphosphatemia, a class-specific adverse event, was the most common all-grade toxicity with an incidence of 60%. Sixty-four percent of patients developed grade ≥3 adverse events: hypophosphatemia (12%), arthralgia (6%), stomatitis (5%), hyponatremia (5%), abdominal pain (5%), and fatigue (5%). Forty-five percent of patients experienced severe toxicity, with the most common events being abdominal pain (5%), pyrexia (5%), cholangitis (3%), and pleural effusion (3%). No deaths were considered treatment related.

Based on such results, one can undoubtedly agree with the FDA's decision to approve pemigatinib for the treatment of such an aggressive tumor, in which the survival of patients who did not respond to first-line therapy previously did not exceed 6.5–13.4 months. Pemigatinib increases this figure by at least 2 times. A phase 3 study FIGHT-302 has been announced and is ongoing [20]. It compares pemigatinib with the combination of gemcitabine and cisplatin as the first-line treatment for metastatic cholangiocarcinoma harboring *FGFR2* gene rearrangements.

The results of an efficacy study of the second FGFR1-3 inhibitor, infigratinib, were presented as a late-breaking abstract at the 2018 ESMO congress [21]. Patients with cholangiocarcinoma, resistant to standard chemotherapy, received oral infigratinib 125 mg daily for 21 days of a 28-day cycle until unacceptable toxicity, disease progression, or consent withdrawal. The primary endpoint was the confirmed overall response rate as assessed by the investigators. The secondary endpoints included progression-free survival, disease control rate, overall survival, and safety.

The study enrolled 71 patients (62% women; median age of 53 years) with *FGFR2* fusion/translocation. The preliminary analysis showed the median treatment duration of 5.5 months and follow-up time of 8.4 months, with 62 patients having discontinued the treatment. The total objective response rate (confirmed and unconfirmed responses) was 31.0%, with the rate of confirmed responses being 26.9%. The rate was higher in patients who received ≤1 prior line of therapy (39.3%) than in patients who received ≥2 lines (17.9%). Disease control was achieved in 83.6% of cases. The response to treatment lasted for 5.4 months on average. The median progression-free survival was 6.8 months. The median overall survival was 12.5 months. The most frequent any-grade adverse events were hyperphosphatemia (73.2%), fatigue (49.3%), stomatitis (45.1%), alopecia (38.0%), and constipation (35.2%). Grade 3–4 toxicity developed in 47 patients (66.2%), including hypophosphatemia (14.1%), hyperphosphatemia (12.7%), and hyponatremia (11.3%). Based on these results, the FDA approved an accelerated phase 3 clinical trial (PROOF 301), in which infigratinib is investigated as the first-line treatment for FGFR2-positive cholangiocarcinoma [22].

Therefore, FGFR2 monotherapy was a 2–3 times more effective therapeutic option with lower toxicity than old-fashion chemotherapy. Moreover, molecular agents have been associated with a higher response rate and prolonged duration of responses. These compounds have opened up an efficient second line of cholangiocarcinoma therapy that was not previously known. There is no doubt that it is necessary to assess the FGFR fusions and rearrangements in routine practice and, if present, to prescribe an FGFR inhibitor. There are a number of other FGFR inhibitors in phase 1 and 1/2 trials, including futibatinib, derazantinib, Debio 1347, and erdafitinib. It can be assumed that FGFR inhibitors will be included in the standards of the first line of therapy in the near future.

IDH Inhibition

Inhibition of IDH is another direction of targeted therapy for metastatic cholangiocarcinoma. An IDH mutation is found in intrahepatic cholangiocarcinoma cells in 10–20% of cases [23, 24]. IDH exists in 3 isoforms, of which IDH1 and IDH2 play the greatest role in carcinogenesis. *IDH1* mutations are more common than *IDH2* mutations. Somatic *IDH1/2* mutations appear in the early stages of tumor development. Increased IDH1/2 activity results in changes in the cellular metabolism and subsequent accumulation of the metabolite 2-hydroxyglutarate, which suppresses cell differentiation and induces tumorigenesis, in both tumor cells and blood. *IDH1/2* mutations are not of prognostic interest; however, they are an excellent target for inhibition.

Ivosidenib, a small molecule inhibitor, inhibits IDH1 in cholangiocarcinoma cells harboring this mutation. Its efficacy has been studied in an international, multicenter, randomized phase 3 trial (ClarIDHy) [25]. Two hundred thirty patients with IHD1-positive metastatic cholangiocarcinoma resistant to standard chemotherapy were assigned in a 2:1 ratio to the ivosidenib (500 mg, orally, daily, 28-day cycle; $n = 124$) or placebo group ($n = 61$). Patients could crossover from placebo to ivosidenib. The primary efficacy endpoint was progression-free survival.

With a median follow-up of 6.9 months, patients treated with ivosidenib had a significantly better progression-free survival than patients treated with placebo (HR = 0.37; $p < 0.0001$). In absolute terms, the median was 2.7 and 1.4 months for this endpoint. The median overall survival was 10.8 months in the ivosidenib group and 9.7 months in the placebo group (HR = 0.69; $p = 0.06$). The 6-month and 1-year survival rates were 67/59% and 59/38%, respectively. The favorable overall survival trend became statistically significant after adjusting for the 70% of patients crossing over to ivosidenib after radiographic disease progression [26]. In that adjusted analysis, risk was reduced by 51% ($p < 0.0001$), and the median overall survival was 10.3 months with ivosidenib compared with 5.1 months with placebo. Two percent of patients achieved response to the inhibitor; there were no objective responses in the placebo group. Ivosidenib showed similar results in a phase 1 extension study ($n = 73$) with the objective response rate of 5% and the median progression-free survival of 3.8 months [27]. As regards the reported toxicity in the ClarIDHy study, ascites (7%) was the most common grade ≥3 adverse event in both groups. Serious toxicity was reported in 30% of ivosidenib-treated patients and 22% of placebo-treated patients. There were no treatment-related deaths. Toxicity leading to treatment discontinuation was more common with placebo (8.5%) than with ivosidenib (6.6%). Health-related quality of life was also improved.

Again, targeted therapy is showing excellent results with a decrease in toxicity. The IDH1 inhibitors reduced the risk of disease progression by 63% and improved the overall survival by 2 times in pretreated patients. Data on progression-free survival and overall survival, combined with an acceptable safety profile and supportive health-related quality of life data, demonstrate the clinical benefit of ivosidenib in this aggressive disease for which there is an unmet need for new therapies.

PD-1/PD-L1 Inhibition

The immune system plays an important role in the pathogenesis of biliary tract tumors [28]. Several studies have shown that PD-L1 expression occurs in half of patients and correlates with a poor prognosis [29]. Immune checkpoint inhibitors have been studied in early clinical trials in patients with biliary tumors. In a multicenter phase 1 study, Japanese patients with biliary tract adenocarcinoma (intrahepatic bile duct cancer, extrahepatic bile duct cancer, gallbladder cancer, or ampullary cancer) and resistance to standard gemcitabine-based treatment regimens received nivolumab monotherapy [30]. A combination of nivolumab with gemcitabine and cisplatin was administered in chemotherapy-naïve patients. In the monotherapy group, the median progression-free survival was 1.4 months and the median overall survival was 5.2 months. In the combination therapy group, the median progression-free survival was 4.2 months and the median overall survival was 15.4 months. One of 30 patients and 11 of 30 patients achieved objective response in monotherapy and combination groups, respectively. The authors concluded that this trial provides supportive evidence for future larger studies of nivolumab in this difficult-to-treat cancer. A phase 2 study evaluated the efficacy and safety of the nivolumab monotherapy in patients with disease progression after 1–3 treatment lines [31]. The primary endpoint was the investigator-assessed objective response rate of 22% (10 of 46 patients), with a disease control rate of 59% (27 of 46 patients) and durable responses over 1 year. The median progression-free survival was 3.68 months and the median overall survival was 14.24 months. Both trials demonstrated better outcomes in patients with PD-L1 expression.

Another checkpoint inhibitor, pembrolizumab, has been studied in phase 1b and phase 2 basket trials [32]. A phase 1b study (KEYNOTE 028) included 24 PD-L1-positive (PD-L1 ≥1%) patients and reported an objective response rate of 13%. The median progression-free survival and the median overall survival were 1.8 and 6.2 months, respectively. The one-year survival rate was 27.6%. In the phase 2 study (KEYNOTE 158), 61 of 104 patients had PD-L1 expression. Despite a 2-fold decrease in the response rate (5.8%) compared to the previous study, the median progression-free survival (2 months), median overall survival (7.4 months), and 1-year survival rate (32.7%) were very similar. Bang et al. [32] concluded that pembrolizumab provided durable antitumor activity, regardless of PD-L1 expression, and manageable toxicity.

Durvalumab alone (n = 42) or in combination with tremelimumab (n = 65) was also investigated in Asian patients with advanced biliary tumors and disease progression on previous systemic therapy [33]. In the durvalumab group, 2 patients had partial responses, and 7 patients had partial responses in the combination group. The disease control rate at 12 weeks was 16.7 and 32.2%, respectively. The median duration of response for the durvalumab group was 9.7 months and 8.5 months for the combination group. The median overall survival was 8.1 and 10.1 months in these groups.

Finally, a randomized, open-label, multicenter phase 2 trial (n = 77) showed activity of atezolizumab (anti-PD-L1 inhibitor) in combination with cobimetinib (MEK inhibitor) in patients with 1–2 lines of prior therapy for biliary tract cancers including cholangiocarcinoma [34]. The trial met its primary endpoint, with a median progression-free survival of 3.65 months and 45.1% of objective responses. Overall survival data were not mature at the time of analysis. Immunotherapy has given hope to patients with cholangiocarcinoma. Preliminary results indicate that this treatment can be successful in this cohort of patients. A phase 3 study is required in which checkpoint inhibitors should be compared with standard chemotherapy.

Conclusions

We are witnessing a revolution in the treatment of cholangiocarcinoma today. The treatment-refractory tumor has begun to lose ground amid treatment with FGFR inhibitors and IDH inhibitors. A total of 25% of patients have molecular genetic alterations that allow considering such therapy. FGFR2 inhibition drastically increased objective response rates, progression-free survival, and overall survival compared with chemotherapy in previously treated patients, serving as the basis for FDA approval of pemigatinib for the second- and subsequent-line therapy. Despite the fact that the results with IDH inhibition seem to be inferior to those with FGFR inhibition, this treatment option is also viable. First, a significant difference in the primary endpoint was achieved in the study, and the risk of disease progression was reduced by 63%; second, patients who have relapsed after prior lines of therapy have no other options; third, IDH-mutant cholangiocarcinoma is a separate tumor type that requires a special approach. Based on the effects of the IDH1 mutation on tumors, for instance, a role in DNA repair, one possibility is to combine IDH1 inhibitors with inhibitors of poly (ADP-ribose) polymerase.

Promising clinical benefit was also observed with immune checkpoint therapy. Apparently, the assessment of PD-L1 expression will not be necessary for the treatment initiation. Nivolumab, pembrolizumab, durvalumab, and tremelimumab showed intriguing results in heavily pretreated patients. Another possible option, based on modulation of the immune microenvironment, is to combine FGFR or IDH1 inhibitors with checkpoint inhibitors. Looking into the future, we can expect the emergence of these drugs in the first-line therapy, as well as investigation of new targets for targeted molecular therapy. At the Hadassah Institute of Oncology, we are conducting a registry study that will help assess the impact of new treatments in routine practice.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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