Therapeutic options for intrahepatic cholangiocarcinoma

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Abstract: Biliary tract cancer (BTC) is a heterogeneous group of cancers, which is composed of intrahepatic cholangiocarcinoma (ICCA), extrahepatic cholangiocarcinoma (ECCA), gallbladder cancers and ampullary carcinomas. While all anatomic subgroups are treated uniformly, our understanding about the pathogenesis has allowed us to reason that each group represents a clinically and genetically diverse disease. The majority of patients present with locally advanced or metastatic disease, where the standard treatment is combination systemic cytotoxic chemotherapy with gemcitabine and cisplatin. While most receive a clinical benefit from chemotherapy, patients eventually progress where no standardized therapies are available in the refractory setting. With the use of next generation sequencing, we have come to understand that ICCA is a diverse genomic disease with many actionable alterations that may serve as potential therapeutic targets. Further studies investigating the role of novel targeted agents (as a single agent or with combination chemotherapy) will hopefully provide additional treatment options for this highly lethal disease.

Keywords: Chemotherapy; targeted therapy; next generation sequencing; intrahepatic cholangiocarcinoma (ICCA); biliary tract cancer (BTC)

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Introduction

Biliary tract cancer (BTC) is composed of a group of neoplasms, which include intrahepatic cholangiocarcinoma (ICCA), extrahepatic cholangiocarcinoma (ECCA), gallbladder cancer and ampullary carcinoma. Although anatomically BTC arise from a contiguous anatomical region, with improved understanding of molecular biology and genetics, it has become evident that this is a very heterogeneous disease. Collectively however, BTC is associated with universally high morbidity and mortality given the diagnosis at a later stage for most (1). In the United States, it is estimated that in 2016 there will be 39,230 new cases and five year survival less than 20% (2).

ICCA is a rare tumor that arises in the peripheral branches of endothelial cells in the biliary tree and accounts for up to 30% of all primary liver malignancies (3,4). It is the second most common primary liver cancer with an increasing incidence over the past few decades, with approximately two-thirds of patients presenting with advanced or metastatic disease (5). Surgical resection is the mainstay for potentially curative therapy in patients with resectable disease. Even with optimal surgery, the 5-year overall survival (OS) and recurrence rates are 15–40% and 50–60% respectively, with a median disease free interval of 26 months necessitating the need for chemotherapy and radiation (6,7). Factors that are associated with survival and tumor recurrence are the presence of multiple primary tumors, vascular invasion and lymph node metastasis. Presence of lymph node positive disease is seen in about 22–37% and is associated with worse outcomes (7,8). Cytotoxic chemotherapy is a standard part of therapy for recurrent or metastatic disease.

Treatment options

Staging and survival of ICCA

ICCA is often diagnosed with locally advanced or metastatic disease. In patients who are diagnosed with early stage disease, the only potential curative treatment is partial hepatectomy (9). Long-term survival at 5-year is reported to be 20–40% following aggressive resection (10). Even with adequate resection, more than 50% of patients experience recurrence of tumor in the first or second year post resection (11). Factors associated with an increased survival after resection include R0 resection, mass-forming tumor types, no lymph node involvement, low tumor burden, CA 19-9 lower than 100 IU/mL, absence of satellite nodules, absence of lymphovascular involvement, and absence of perineural invasion (11).

The Role of adjuvant therapy in resectable or locally advanced ICCA

Given the high incidence of recurrence following adequate resection, adjuvant treatment strategies to diminish the risk of recurrence include chemotherapy and/or radiation. There is a noticeable absence of phase III trials supporting the use of adjuvant therapy in patients following surgical resection. Results of a large multi-center randomized phase III (BILCAP) evaluating the role of adjuvant capecitabine in bile duct or gallbladder cancer are expected in 2017. Currently, treatment strategies are mostly based on trials consisting of BTC from any origin. A recent meta-analysis evaluated the role of adjuvant chemotherapy, chemoradiation, or radiation in BTC (12). The study suggested that patients who received either chemotherapy or chemoradiation had a better outcome than those who received radiation alone [odds ratio (OR) 0.39, 0.61, and 0.98, respectively; P=0.02]. A sub-group analysis showed that patients who had lymph node positive disease (OR 0.49; P=0.004) and R1 resection (OR 0.36; P=0.002) had the greatest benefit with chemotherapy or chemoradiation as adjuvant therapy. However, ICCA was underrepresented with only 11 of 6,700 cases were of primary intrahepatic disease.

Consistent with the findings above, another study suggested that adjuvant therapy might benefit patients with adverse prognostic features (lymph node metastasis or blood vessel invasion). In this study, patients who received adjuvant therapy with gemcitabine, 5-fluorouracil (5-FU) and cisplatin (GFP) had a longer progression-free survival (PFS) at 1 year compared to those who did not (71.6% *vs.* 45%, P<0.02) (13). Similarly, another retrospective review of the role of adjuvant therapy in patients who had an R0 resection for intrahepatic and perihilar cholangiocarcinoma was recently conducted (14). In this study, 80 patients (58.4%) had ICCA and 35 patients (25.5%) had lymph node involvement. A total of 73 (53.3%) of patients received adjuvant therapy with chemotherapy, chemoradiation or radiation alone. The authors found that lymph node involvement (HR: 3.60; P<0.001), tumor differentiation (HR: 2.35; P=0.048) and an elevated baseline CA 19-9 (HR: 1.97; P=0.013) were all predictors of worse OS. Patients who received adjuvant chemoradiation had a longer recurrence free survival (RFS) (HR: 0.44; P=0.036) but no benefit in OS (HR: 0.56; P=0.245) in lymph node negative disease. However, there was a numerical trend for improvement in OS with adjuvant chemoradiation in patients with lymph node positive disease (HR: 0.24; P=0.097). In contrast chemotherapy alone did not appear to improve RFS or OS, and radiation therapy was associated with a shorter RFS and OS. Review of this data, suggests that the addition of radiation to chemotherapy may provide a benefit in patients with an R0 resection and lymph node positive disease, however prospective studies will need to determine the validity of this observation.

To better understand the role of radiotherapy following surgical resection, another analysis on patients from the National Cancer Database [1998–2011] was performed (15). In this retrospective analysis, a total of 405 patients were stratified based on resection margin status. Survival for R0 *vs.* R1/R2 was 32 *vs.* 16.5 months respectively (P<0.001) and radiotherapy appeared to have a trend in improved survival for R1/R2 thought not significant (P=0.191). Furthermore, in a multivariable model accounting for age, sex, comorbidities, disease stage and resection margins, radiotherapy did not appear to be a predictor for improved survival. The authors from this study concluded that radiotherapy alone does not significantly impact survival in patients with positive margins.

Liver transplantation

The role of liver transplantation in ICCA remains highly controversial with conflicting published data. ICCA has been consistently shown to have a 20–40% OS at 3–5 years after liver transplant in numerous studies. Though it is not currently an established indication for liver transplantation, it represents a potential curative option for those who do not meet strict criteria for resection (16-18). The Mayo protocol consisting of the combination of neoadjuvant

chemoradiation with 5-FU followed by brachytherapy with 5-FU has been shown to have significant improvements, where 92% of patients are disease free at 37 months (19). Hong *et al.* described improved outcomes with the use of neoadjuvant/adjuvant chemotherapy combined with liver transplantation for ICCA (20). The authors divided patients in to three categories (low, intermediate, high) based on a prognostic scoring system composed of seven clinico-pathological risk factors (multifocal tumor, perineural invasion, infiltrative subtype, lack of neoadjuvant and/or adjuvant therapy, history of primary sclerosing cholangitis, hilar cholangiocarcinoma and lymphovascular invasion). The authors reported a 5-year RFS rate of 78% in low risk group, compared with 19% in intermediate, and 14% in high risk groups, suggesting that liver transplant is appropriate in select cases of locally advanced ICCA. More recently, a retrospective multicenter study demonstrated that liver transplantation for select cirrhotic patients with small solitary lesions (up to 2 cm) achieved a 5-year survival rate of 73% (21). Furthermore, at a median follow-up of 36 months, none of the patients had a tumor recurrence. While the data is inconclusive about the role of orthotopic liver transplantation (OLT) in patients with ICCA, but given its curative intent, liver transplantation seems as a reasonable option in ideal patients who are fit with good performance status, minimal co-morbidities and of young age. Prospective, randomized clinical trials are needed to confirm the benefits of OLT in ICCA. At least for now, we know that patients with vascular and/or lymphatic invasion and/or tumor size larger than 2 cm are likely to have a higher recurrence rate and may not benefit from OLT (22).

Therapy options for unresectable disease

In patients who present with advanced or metastatic disease, systemic chemotherapy is a standard approach in the treatment of ICCA. The Advanced Biliary Cancer (ABC-02) Trial, the largest randomized phase III study conducted in BTC, evaluated the combination of gemcitabine with or without cisplatin. Patients had a diagnosis of unresectable, recurrent, or metastatic BTC that included intrahepatic or exhepatic cholangiocarcinoma, gallbladder cancer and ampullary carcinoma. The study demonstrated that the addition of cisplatin significantly improved both PFS (8 months compared to 5 months; HR: 0.63; 95% CI: 6.6–8.6; P=0.001) and OS (11.7 months compared to 8.1 months; HR 0.64; 95% CI: 0.52–0.80; P=0.001) (23). The survival benefit was significant in all sub-groups including patients with ICCA. Similar results were observed in a Japanese randomized phase II trial (24). Based on this data, the combination of gemcitabine + cisplatin is now the current standard of care for first line therapy.

Further number of phase II studies suggested that oxaliplatin added to gemcitabine (GEMOX) may have comparable historical outcomes than cisplatin with a range of reported OS of 8.3 to 11 months (25-29). A recent randomized phase II trial suggested that GEMOX may be superior to 5-FU or best supportive care (BSC) alone (OS 9.5 *vs.* 4.5 *vs.* 4.6 months respectively, P=0.032) (30). Moreover, a pooled analysis done by Eckel *et al.* (31) suggested that chemotherapy with gemcitabine combined with cisplatin or oxaliplatin increases the response rate and tumor control rate in cholangiocarcinoma. A number of smaller studies evaluated the role of numerous chemotherapies in combination with gemcitabine and were shown signs of interesting activity with response rates approximately ranging between 20% and 40% (32-35) (*Table 1*).

Second-line therapy

In patients who progress on gemcitabine and platinum based therapy, there is no standard option. Several trials evaluating regimens for ICCA in the second-line setting show promising activity (*Table 2*). Though all of the trials had few patients, mOS had ranged from 4–9 months suggesting that treatment in the refractory setting is feasible and safe, and may provide a survival advantage over BSC.

Emerging molecularly targeted therapy

Cytotoxic chemotherapy is effective and provides a benefit in the majority of patients, however its efficacy is short-lived and all patients will eventually develop resistance. With better understanding of tumor biology and molecular pathways involved in ICCA, the use of novel, targeted agents is at the forefront and provides additional treatment options. Targeted therapies are more likely to be selective for malignant cells, thus result in better efficacy and perhaps better tolerability. With the use of next generation sequencing, there is a better understanding of the landscape of ICCA.

Table 1 Summary of first line chemotherapy trials in advanced BTC

Study	Phase	Treatment arms	OS (months)	P value
Glimelius *et al.*, (36)	II	5-FU/etoposide *vs.* BSC	6 *vs.* 2.5	<0.0100
Takada *et al.*, (37)	II	5-FU/doxorubicin/mitomycin-C *vs.* BSC	6 *vs.* 3	*NR
Sharma *et al.*, (30)	II	BSC vs 5-FU *vs.* GEMOX	4.5 *vs.* 4.6 *vs.* 9.5	0.0320
Kornek *et al.*, (33)	II	Mitomycin-C/gemcitabine *vs.* mitomycin-C/ capecitabine	6.7 *vs.* 9.3	*NR
Ducreux *et al.*, (38)	II	5-FU *vs.* cisplatin/5-FU	5 *vs.* 8	*NR
Rao *et al.*, (39)	III	5-FU/etoposide *vs.* epirubicin/cisplatin/5-FU	12 *vs.* 9	0.2059
Valle *et al.*, (23)	III	Gemcitabine/cisplatin *vs.* gemcitabine	11.7 *vs.* 8.1	<0.0010
Okusaka *et al.*, (24)	II	Gemcitabine/cisplatin *vs.* gemcitabine	11.2 *vs.* 7.7	*NR

BTC, biliary tract cancer; OS, overall survival; 5-FU, 5-fluorouracil; BSC, best supportive care; *NR, not resulted; GEMOX, gemcitabine + oxaliplatin.

Table 2 Summary of second line therapies in treatment refractory BTC

Study	Phase	Treatment arms	OS (months)	PFS (months)
Oh *et al.*, (40)	II	Gemcitabine	4.1	1.6
Lee *et al.*, (41)	II	Continuous 5-FU, doxorubicin, and mitomycin-C	6.7	2.3
Sasaki *et al.*, (42)	Feasibility	Gemcitabine/cisplatin*	5.9	3.6
Paule *et al.*, (43)	II	GEMOX + cetuximab	7.0	4.0
Chiorean *et al.*, (44)	I	Erlotinib and docetaxel	5.7	4.0
Lim *et al.*, (45)	I	5-FU, doxorubicin, and mitomycin-C	5.6	2.2
Sasaki *et al.*, (46)	Pilot	Irinotecan	6.7	1.8
He *et al.*, (47)	I	Oxaliplatin, 5-FU, and leucovorin	NR	3.1
Yi *et al.*, (48)	II	Sunitinib	NR	1.7
Buzzoni *et al.*, (49)	II	Everolimus	7.7	3.2
Denlinger *et al.*, (50)	II	Bortezomib	9.0	5.8
Roth *et al.*, (51)	II	Imatinib[#]	NR	NR

*, patients refractory to gemcitabine and S-1; [#], trial stopped early due to poor recruitment and no responses were seen in the intention to treat population; BTC, biliary tract cancer; OS, overall survival; PFS, progression-free survival; 5-FU, 5-fluorouracil; NR, not resulted; GEMOX, gemcitabine + oxaliplatin.

Epidermal growth factor receptor (EGFR) inhibitors

EGFR is an extracellular receptor tyrosine kinase that when bound to its ligand causes a downstream autophosphorylation leading to activation of intracellular signaling cascades. It is overexpressed in 10–32% of patients ICCA. Overexpression of this pathway promotes intracellular activity, resulting in cell proliferation, angiogenesis and evasion of apoptosis (52). In patients with ICCA, increased activation of EGFR is associated with impaired OS and associated with presence of lymph node metastasis (53).

Erlotinib is an oral, reversible tyrosine kinase inhibitor

that inhibits activation of EGFR. An initial study suggested that erlotinib monotherapy has interesting activity in BTC (54). However, when combined with other agents, the results have been relatively disappointing. The addition of erlotinib to GEMOX or bevacizumab was mostly disappointing and not historically much different than GEMOX or bevacizumab alone (55,56).

Cetuximab and panitumumab are EGFR directed monoclonal antibodies. An initial single arm study suggested a potential survival benefit with panitumumab, where the combination of gemcitabine, irinotecan and panitumumab in patients with cholangiocarcinoma resulted in a median PFS of 9.7 months and OS of 12.9 months (57). However, a large, randomized phase II trial, BINGO, failed to confirm the efficacy of anti-EGFR monoclonal antibodies, where the combination of cetuximab with gemcitabine and oxaliplatin failed to improve patient outcomes (58). This was a small, non-randomized study and future randomized studies are needed to better understand the role of anti-EGFR therapy. Similar disappointing findings were observed when panitumumab was combined with GEMOX followed by capecitabine in patients with ICCA or ECCA who were *KRAS WT* (59).

Human growth factor receptor 2 (HER-2/neu) as a target

HER-2/neu promotes cell growth, survival and motility. When amplified or overexpressed, *HER-2/neu* has been shown to have a pivotal role in the development and progression of solid tumor malignancies in general. Inhibition of *HER-2/neu* has been shown to be effective in gastric and breast cancers (60,61); however this has not been demonstrated in BTC. There have been two phase II trials evaluating lapatinib as monotherapy in biliary malignancies suggesting no meaningful activity observed (62,63). Contrarily, results from My Pathway study, from ASCO, evaluated six patients with *HER-2/neu* amplification or overexpression and found a clinical benefit in all patients (50% CR/PR, 50% with SD >120 days). This is a small study and prospective studies need to be done to validate these findings.

Vascular endothelial growth factor (VEGF) inhibitors

VEGF pathway is a potent stimulator of angiogenesis, highly expressed in BTCs and associated with a more aggressive phenotype (64). Bevacizumab is a humanized monoclonal antibody which inhibits VEGF and has been evaluated in BTC. A single arm phase II study of bevacizumab with GEMOX in patients with advanced BTC showed a median PFS of 7 months and OS of 12.7 months (65). These findings suggested that targeting VEGF might be a potential relevant therapeutic strategy in BTC. Based upon these results, ABC-03, a randomized phase II trial was conducted investigating the combination of chemotherapy with or without cediranib, an oral VEGF receptor inhibitor in patients with advanced biliary cancer, with its primary endpoint being PFS. One hundred and twenty four patients were enrolled in this study, of which 29 patients had ICCA (14 in cediranib and 15 in placebo). The results, unfortunately, were disappointing with no significant difference observed between the two arms (8 months in cediranib *vs.* 7.4 months in placebo; P=0.72) (66). Currently, VEGF inhibition does not appear to be a relevant therapeutic target in BTC. Furthermore, a recent randomized phase II study evaluated VEGF *vs.* EGFR inhibition with combination chemotherapy in patients with *KRAS WT* non-resectable BTC (67). In this study, patients were randomized to either bevacizumab or panitumumab in a crossover design. The study showed no significant difference in the blockade of either target.

MET inhibitors

The binding of hepatocyte growth factor (HGF) to its receptor (c-MET) activates signaling through pathways such as *RAS/MAPK* and *PI3K/AKT* that are important in proliferation and survival of tumor cells. Gene expression profiling revealed that c-MET overexpression is found in 20–60% of patients with ICCA and is associated with poor prognosis (68). Further, there is some suggestion that overexpression of c-MET can lead to EGFR resistance; thus leading to the use of c-MET inhibitors in cholangiocarcinoma (69). A recent study evaluated the combination of tivantinib (ARQ 197) with gemcitabine in patients with solid tumors (70). In this study, 20% of the patients achieved a partial response including one patient with cholangiocarcinoma. Another trial evaluated the use of cabozantinib in 19 cholangiocarcinoma patients where c-MET expression was unknown and found no objective responses (71). Overall, the role of inhibitors of c-MET is unknown in this ICCA.

Isocitrate dehydrogenase (IDH) inhibitors

A mutation in isocitrate dehydrogenase 1/2 (IDH1/2)

Table 3 Summary of ongoing trials with targeted agents involving BTC

Treatment—drug name	Target	Clinical trial phase	NCT trial number
AG-881	IDH1/2	I	NCT02481154
AG-120	IDH-1	I	NCT02073994
IDH-305	IDH1R132	I	NCT02381886
BAY1436032	IDH1-R132	I	NCT02746081
ARQ-087	FGFR2	I/II	NCT01752920
BGJ-398	FGFR2	II	NCT02150967
LDK-378	ROS1 overexpression	II	NCT02374489
RXDX-101	NTRK 1/2/3, ROS1, or ALK	II	NCT02568267
Dabrafenib + trametinib	BRAF + MEK	II	NCT02034110

BTC, biliary tract cancer; IDH1/2, isocitrate dehydrogenase 1/2; FGFR2, fibroblast growth factor receptor 2; ROS1, proto-oncogene tyrosine-protein kinase ROS; ALK, anaplastic lymphoma kinase.

causes formation of onco-metabolites that reduce alpha-ketoglutarate to 2-hydroxyglutarate leading to altered cell maturation, differentiation and survival. IDH1 and 2 mutations exist in numerous tumors and were recently identified in BTC. Further, IDH1/2 were evaluated in a large cohort of ICCA patients and was found to be associated with better OS (72). In contrast, patients with cholangiocarcinoma and IDH1/2 mutations had shorter OS compared to those who are wild type (3-year survival of 33% in IDH mutants *vs.* 81% in IDH wild-type) (73). The frequency of these mutations ranges from 22–36% in ICCA and is associated with clear cell or poorly differentiated histology (74,75). Pre-clinical studies suggest that IDH mutations inhibit hepatocyte differentiation, induce proliferation of hepatic progenitors and ultimately leading to the development of premalignant lesions (76). IDH inhibitors are currently being evaluated in clinical trials (*Table 3*).

Fibroblast growth factor receptor (FGFR) inhibitors

Fibroblast growth factor receptor 2 (FGFR2) is a member of the FGFR and is associated with cell differentiation, proliferation and apoptosis (77). Recently with the use of whole exome sequencing, FGFR2 alterations were identified in 6–50% of ICCA (78). Alterations in FGFR2 pathway occur in 13% of patients with ICCA and are associated with improved survival (79). Pre-clinical data and isolated case reports suggest that there is anti-tumor activity with FGFR inhibition; however, the therapeutic benefit it currently unknown. Recently, it was reported that patients with FGFR mutated disease had similar response with first line chemotherapy as those without *FGFR* mutation (80). The authors also reported that when patients were treated with FGFR directed inhibitors after failure of first-line chemotherapy; those with FGFR mutation had a superior OS (P=0.010). A recent study reported results of BGJ398 (a oral small molecule pan-FGFR inhibitor) in patients who failed or were intolerant to platinum-based therapy (81). Of the 22 patients who were evaluable at the time of analysis, 3 achieved a partial response, 15 patients had stable disease and overall disease control rate was 82%. This suggests that ICCA patients with FGFR mutations may have a benefit from treatment with an FGFR inhibitor.

ROS1 inhibitors

ROS1 is a proto-oncogene belonging to the subfamily of tyrosine kinase receptors and increased expression can be seen in up to 9% of patients with ICCA (82). Preclinical data shows that inhibition of *ROS1* can lead to potent anti-tumor effects (83). The benefit of *ROS1* inhibition has been confirmed in non-small lung cancer (84). Similar studies are needed in patients with ICCA to confirm the benefit of targeted therapy in patients *ROS* fusions.

BRAF inhibitors

BRAF is a proto-oncogene, which is involved in directing cell growth. The incidence of BRAF mutations in ICCA has been reported to be about 5% (85). Its presence is associated with a more aggressive phenotype, higher tumor stage and likelihood of lymph node involvement at diagnosis (86). At this time, the benefit of BRAF inhibition with small molecules is unknown but could represent an interesting treatment option, especially in combination with other targeted therapies.

Conclusions

Patients with early stage ICCA and adverse prognostic features may benefit from adjuvant chemotherapy with a possible added benefit from radiation therapy. For locally

advanced or metastatic ICCA standard treatment consists of the combination of gemcitabine with cisplatin. With the use of next generation sequencing, actionable alterations have been identified and can be matched with molecularly targeted therapies that hold promise to improve outcomes. Future trials will continue to focus on dissecting the molecular landscape of ICCA to identify novel potential therapeutic targets. As newer therapies emerge, it will be important to identify potential biomarkers that will help select patients who are most likely to benefit from combined therapy.

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Footnote

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