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Cholangiocarcinoma SUMMIT™

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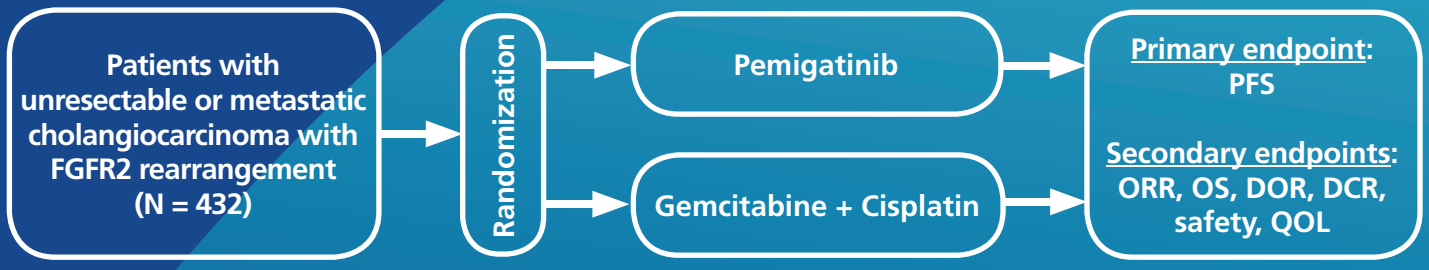

Select inclusion criteria:

- Age ≥18 years
- Histologically or cytologically confirmed cholangiocarcinoma that is previously untreated and considered unresectable and/or metastatic
- Radiographically measurable/evaluable disease by CT or MRI per RECIST v1.1 criteria
- ECOG PS 0 to 1
- Documented FGFR2 rearrangement

Select exclusion criteria:

- Received prior anticancer systemic therapy for unresectable and/or metastatic disease (not including adjuvant/neo-adjuvant treatment completed at least 6 months prior to enrollment, and treatment for locally advanced disease with clear evidence of radiological progression)
- Child-Pugh B and C
- Current evidence of clinically significant corneal or retinal disorder confirmed by ophthalmologic examination
- History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissue

The efficacy and safety of the investigational compounds discussed have not been established.

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CCA, cholangiocarcinoma; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FGFR, fibroblast growth factor receptor; FIGHT, Fibroblast Growth Factor Receptor Inhibitor in Oncology and Hematology Trials; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors

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Cholangiocarcinoma SUMMIT™

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Updates on the Understanding of Cholangiocarcinoma

On October 17 and 18, 2019, a group of international experts convened in Phoenix, AZ, for the First Annual Cholangiocarcinoma Summit. The goal of the meeting was to discuss the latest clinical data on the disease, as well as the implications of these findings for providers and patients. Each topic included in the summit was presented by 2 speakers and then analyzed by a chorus of experts in the field. This format was chosen to provide a consensus, whenever possible, on each topic that was presented.

This publication provides highlights of key presentations and discussions from the meeting. In this first article, we discuss the epidemiology of cholangiocarcinoma (CCA), the role of aspirin and statins as chemoprevention, the molecular and genetic pathogenesis of the disease, treatment strategies, urgent clinical needs, and the latest hot topics.

Epidemiology of Cholangiocarcinoma

CCA, also known as bile duct cancer, is a rare malignancy that is diagnosed in approximately 8000 individuals in the United States each year.[1] The peak age at presentation is in the seventh decade of life.[2] The intrahepatic form of CCA is the second most common primary liver tumor after hepatocellular carcinoma (HCC).

The epicenter of CCA is Thailand and nearby regions, where the most common predisposing cause is believed to be liver fluke infection. In contrast, in the Western world, the most common predisposing cause of the disease is primary sclerosing cholangitis (PSC).[3] The global variation in incidence not only reflects differences in genetic factors, but also the "exposome," which has been defined as the collection of environmental factors to which one has been exposed over his or her lifetime.[4]

The incidence of intrahepatic CCA worldwide has been increasing, a pattern that began decades ago, whereas the incidence of extrahepatic CCA has remained stable or has been on the decline. Overall, the incidence of CCA is on the rise. The reported trends in CCA incidence should be interpreted with caution, however, because current coding systems do not consider the accurate recording of CCA data and thus may contribute to the reported rise in intrahepatic CCA.

International consistency and accuracy in the topographic classification of CCA are needed to allow accurate monitoring of disease rates. The belief is that bile duct cancers should be subclassified as intrahepatic, perihilar, or distal,[5] and that *International Classification of Diseases, 11th Revision*,[6] and subsequent iterations of *International Classification of Diseases for Oncology* should have separate topography and morphology codes for each of these 3 cancer subtypes.[7] To improve the collection of data, healthcare professionals must ensure that the correct code is recorded at tumor boards, in clinical case notes, and on death certificates, and that administrative teams are appropriately trained in the assignment of codes.

Regardless of the way in which CCA is classified, its incidence appears to be increasing, thus warranting more studies regarding the cause of the disease, as well as more effective therapies.

Aspirin and Statins as Chemoprevention

Given the known anti-inflammatory effects of aspirin and statins, investigators have studied the potential role of these agents in the prevention of biliary tract cancers. A hospital-based, case-control study demonstrated that aspirin use was significantly associated with a 2.7-fold to 3.6-fold decreased risk for the 3 subtypes of CCA.[8]

Findings from a population-based cohort study derived from 3 Swedish registries suggest that the use of low-dose aspirin and statins decreases the risk for biliary tract cancer in a subtype- and sex-dependent manner.[9] The investigators in this study reported that among women, a nonsignificant decrease in the risk for extrahepatic CCA was observed with aspirin use alone. Furthermore, statin use alone significantly reduced the risk for extrahepatic CCA in women by 40% and in men by 53%. Moreover, women who were exposed to aspirin alone, a statin alone, or both had a 24% to 28% reduction in the risk for gallbladder cancer. Among men, although the estimates did not reach statistical significance, the estimates for use of a statin alone and the combined use of low-dose aspirin and a statin suggested protection against gallbladder cancer.[9]

A meta-analysis of 4 case-control studies and 1 retrospective cohort study showed that aspirin users are less likely to develop CCA compared with aspirin nonusers (odds ratio, 0.56).[10] The definition of aspirin use in each study differed, however, with only 1 study considering an individual with a duration of use of ≥6 months to be an aspirin user. Although these studies suggest a favorable chemopreventive effect of aspirin, it cannot be concluded that aspirin reduces the risk for CCA.

Studies have demonstrated no consistent effect of statin use on the development of CCA. This finding is supported by a meta-analysis of 27 randomized controlled trials that failed to show an association between statin use for >2 years and the risk for several types of cancers.[11]

CHORUS DISCUSSION

The lack of rigor in describing biliary tract cancers was recognized by the chorus of experts. In addition to the 3 distinct topographic and morphologic forms of CCA, biliary tract cancers comprise gallbladder cancer and ampullary cancer, all of which behave differently. Distinguishing among these various forms of biliary tract cancer is important when interpreting the results of clinical trials.

A member of the chorus noted the difficulty involved in discriminating between ampullary cancer and extrahepatic CCA, indicating that approximately 5% of patients enrolled in the Advanced Biliary Tract Cancer (ABC)-02 trial[12] had ampullary cancer that had been misdiagnosed as biliary tract cancer. The International Rare Cancers Initiative is assessing the biology of rare cancers (<2/100,000), such as cancer of the ampulla of Vater, to facilitate the development of international clinical trials for these malignancies. "Only in that way can you distinguish between a ductile pancreatic cancer, a bile duct cancer, and a small bowel cancer," said one of the chorus members.

In addition, HCC is often present at the diagnosis of carcinoma of unknown primary origin. According to one of the chorus members, ≤10% of HCC tumors are combined HCC and CCA, which may have been overlooked because of a historical reluctance to biopsy HCC. Many cases of CCA are treated as local disease at nonspecialized centers. A movement is underway in the United Kingdom to have every diagnosed case of CCA reviewed at a regionally recognized hepatobiliary center that has appropriate expertise in oncology, radiology, and surgery.

In terms of chemoprevention, one chorus member requested a randomized controlled trial of aspirin versus placebo in patients with PSC, because the ability to demonstrate a benefit from prophylactic therapy is often greater in populations at higher risk. The consensus was that the risk for CCA in a patient with PSC is 0.5% to 1.0% per year, with a lifetime risk of ≤20%.

Molecular and Genetic Pathogenesis of Cholangiocarcinoma

Inflammation and immune response pathways are involved in the pathogenesis of CCA. Whereas obesity is recognized as a significant risk factor for HCC, its contribution to the risk for CCA is underrecognized. In case-control studies, excess weight or obesity in early adulthood is associated with an increased risk for intrahepatic CCA, particularly among women, compared with normal-weight individuals. Obesity is also negatively correlated with the age of onset of intrahepatic CCA.

Chronic inflammation plays an important role in the relationship between obesity and cancer. Genes involved in the inflammatory pathway are candidate genes for susceptibility to cancer. Those genes in the inflammatory pathway that are linked to the development of CCA include *COX-2* and *WRAP53*.

Genetic variations in lipid metabolism pathways may also predispose individuals to the risk for CCA, as the prevalence of G alleles of *PNPLA3* among patients with CCA is similar to that observed in patients with HCC.

Molecular profiling of nonfluke-related intrahepatic CCA reveals that mutations in *IDH1/2*, *BAP1*, and *PBRM1* are more common in Western countries than in Asian regions. Conversely, mutations in *TP53* are found more frequently in Asian regions.

Mutations in *IDH1/2* and *BAP1* are prevalent regardless of CCA subtype, whereas mutations in fibroblast growth factor receptor 2 (*FGFR2*) are more common in intrahepatic CCA versus perihilar and extrahepatic CCA. In addition, mutations in *SMAD4*, *TP53*, and *KRAS* are observed more frequently in perihilar and extrahepatic CCA. Few sequencing studies have been conducted in patients with fluke-positive CCA, but available data show that mutations in *TP53* are highly prevalent (**Figure 1**).

In addition to genetic mutations, focal copy number aberrations, such as deletion of *CDKN2A* and amplification of cyclin D1, have also been found in patients with CCA and are associated with expected changes in gene expression. The dysregulation of *CDKN2A* commonly found in patients with CCA suggests a targetable pathway, perhaps through CDK4/6 inhibition.

Mixed and combined intrahepatic CCA/HCC was recently found to have monoclonal origins. Cancer-specific mutations can exist in both intrahepatic CCA and HCC regions (ie, *IDH1* and *CTNNB1*) of the same tumor sample.[13]

The genomics suggest that CCA is pharmacologically actionable, but additional research is warranted to reveal novel vulnerabilities.

Treatment Strategies for Cholangiocarcinoma

The rationale for biliary drainage in CCA is to relieve obstructive symptoms, minimize obstruction of the future liver remnant (FLR) for resection candidates, reduce the risk for postoperative liver failure, and relieve

cholestasis, which may increase hepatic toxicity and impair postoperative liver regeneration.

Several techniques are available for achieving biliary drainage in patients with CCA. Endoscopic retrograde cholangiopancreatography (ERCP) with dual stenting (usually plastic) is the standard drainage technique for patients with hilar CCA. Endoscopic ultrasound (EUS)-guided intrahepatic biliary drainage of the left lateral lobe can be considered in patients who are not good candidates for percutaneous drainage. EUS-guided drainage can be combined with ERCP stenting.

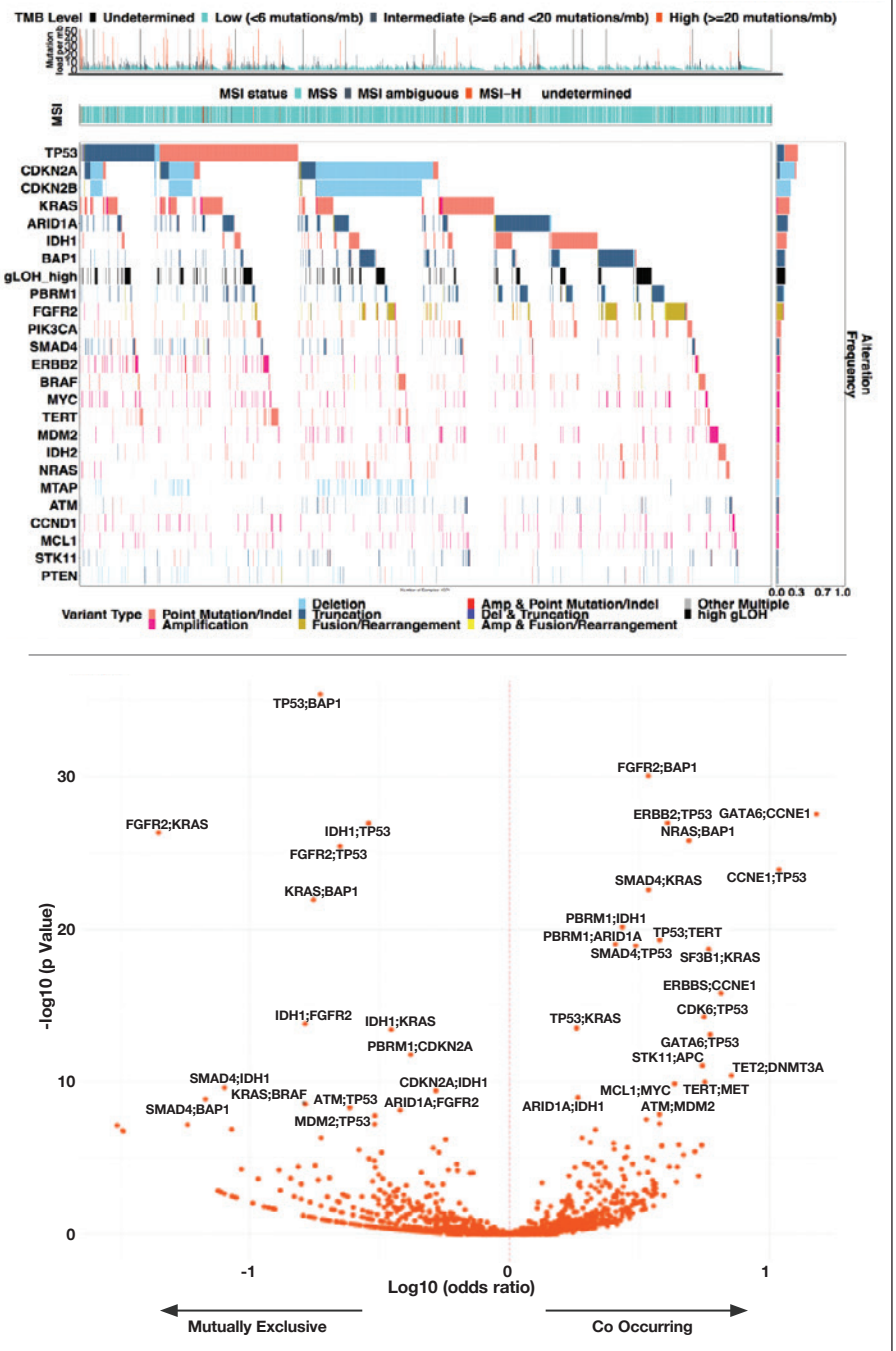
Endoscopic biliary drainage is preferable to percutaneous drainage, because of the relatively high recurrence rate of CCA in percutaneous transhepatic biliary drainage fistulae.[14] Percutaneous drains are avoided in patients with PSC who are candidates for transplant.

Surgical strategies for patients with CCA differ according to subtype. In patients with distal CCA, the surgery resembles a Whipple procedure, whereas those with intrahepatic CCA are managed with liver resection and those with hilar CCA are treated with liver resection plus bile duct resection. All these surgical procedures should include portal lymphadenectomy and selective distant nodal sampling.

A study showed that among patients with perihilar CCA who underwent liver resection, an FLR volume of <30% predicted higher rates of postoperative mortality compared with higher FLR volumes. Complete preoperative biliary drainage improved 90-day mortality in patients with intermediate (30%-50%) FLR volume compared with those with incomplete drainage. In contrast, no postoperative mortality was observed in undrained patients with FLR volumes of >50%.[15] A separate study showed that preoperative cholangitis in the setting of an FLR volume of <30% increased the risk for hepatic insufficiency, liver failure, and death compared with no preoperative cholangitis (**Figure 2**).[16]

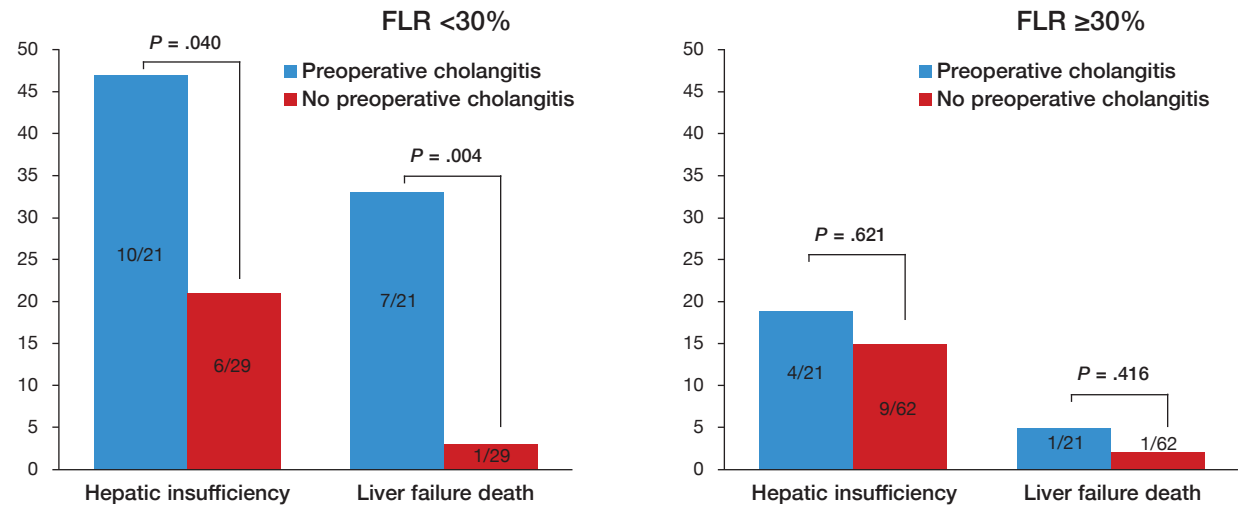
For patients with intrahepatic CCA, although surgery is extremely effective for local tumor control, it is curative in only a minority of individuals. Therefore, the development of more effective adjuvant treatments is critically important in this population. Among patients with hilar CCA or distal CCA, the pattern of spread tends to be locoregional, but the margins are almost

Figure 1 **Profiling of cholangiocarcinoma to identify genomic alterations, tumor mutational burden, and genomic loss of heterozygosity.**



gLOH indicates genomic loss of heterozygosity; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; TMB, tumor mutational burden.

Figure 2 Effect of cholangitis on early postoperative outcomes in patients with future liver remnant volume <30% and ≥30%.



FLR indicates future liver remnant.

always close, and an isolated nodal recurrence pattern is common.

In patients with intrahepatic CCA, mortality from primary tumors that are not resected results from the tumor causing portal venous and hepatic venous occlusions, as well as occlusions and obstructions of the biliary tree, leading to atrophy and eventual liver failure.[17] In those with hilar CCA, relentless episodes of cholangitis, regardless of the use of effective nonoperative therapy, is the leading cause of death.[16]

In patients with unresectable liver disease, the use of local therapies is more critical if the tumor occludes the hepatic vein/inferior vena cava confluence and the portal vein and biliary bifurcation. Ablative doses of external beam radiation therapy are more effective than palliative doses in extending survival in patients with unresectable biliary cancers. Patients who receive insufficient doses of localized radiation that lead, in turn, to poor local tumor control typically die from liver failure related to the primary tumor.

What Are the Most Urgent Clinical Needs in Cholangiocarcinoma?

Patient perspectives

Patients with CCA have identified several urgent clinical needs, including earlier and improved diagnostics, more specialists, and timely results following scans. They also want better access to resources immediately following diagnosis; these resources should explain CCA and its treatments, as well as how to participate in clinical trials.

A survey of >1000 patients with CCA revealed that 30% would be willing to undergo surgery or transplantation even if the risks for complications, including death, were high. Half of the patients surveyed indicated that they would undergo surgery if it increased their likelihood of survival to ≥2 years, and approximately 20% said that they would undergo surgery if it improved their chance of surviving 3 to 12 months. Furthermore, 50% of patients reported that they would be willing to undergo surgery even if there was no chance for a cure.[18]

Patients also want access to experts for second opinions related to early molecular profiling, clinical trials, and treatments. In the above-mentioned survey, >90% of patients viewed molecular profiling as an important, necessary part of their treatment plan. Patients also indicated that they wanted a healthcare provider who thinks outside the box, views each patient as an individual, is willing to tailor a treatment plan to them, and would take risks with their treatment plan. Nearly 80% of patients reported that they would be willing to try a treatment even if there was no guarantee of it helping them, and 85% said that they would enter a clinical trial that had a high risk but the potential for improved outcomes.[18]

Nurse perspectives

Nurses have identified the need for consistency regarding discharge instructions, as well as better instructions for patients receiving biliary stents and drains. Patient quality of life is negatively affected by a lack of adequate knowledge regarding the care of stents and external bil-

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Key eligibility criteria*

- Participants must have histologically or cytologically confirmed locally advanced or metastatic BTC and an ECOG PS of 0 or 1. Participants must have had disease progression on or be intolerant to first-line platinum-based therapy

Key exclusion criteria*

- Participants must not have ampullary cancer and must not have received prior immunotherapy or therapy with immune checkpoint inhibitors

INTR@PID BTC 055[2]

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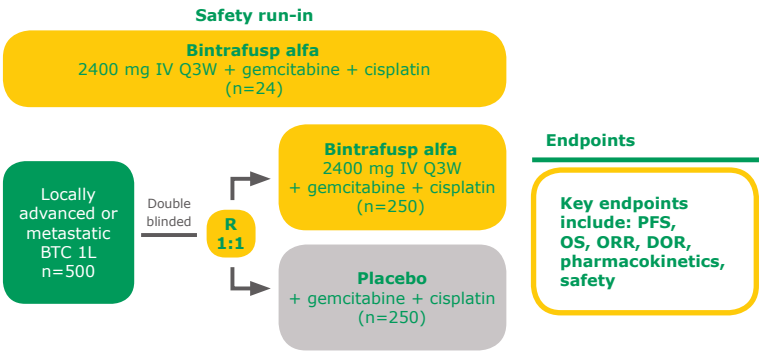
INTR@PID BTC 055 (NCT04066491) is a phase 2/3, global, multicenter, randomized, placebo-controlled study evaluating bintrafusp alfa with gemcitabine plus cisplatin in the first-line treatment of patients with locally advanced or metastatic BTC.

Study Design | Global



Key eligibility criteria*

- Participants must have histologically or cytologically confirmed, locally advanced or metastatic BTC, naive to chemotherapy and immunotherapy, and an ECOG PS of 0 or 1

Key exclusion criteria*

- Participants must not have received organ transplants, including allogeneic stem cell transplants, with the exception of transplants that do not require immunosuppression, and must not have received prior therapy with immune checkpoint inhibitors

* For a full list of all inclusion and exclusion criteria, please visit www.clinicaltrials.gov.

1L, first-line; 2L, second line; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized; TGF-β, transforming growth factor β.

1. ClinicalTrials.gov. M7824 Monotherapy in Locally Advanced or Metastatic Second Line (2L) Biliary Tract Cancer (Cholangiocarcinoma and Gallbladder Cancer). https://clinicaltrials.gov/ct2/show/NCT03833661. NCT03833661. Accessed July 22, 2019. 2. ClinicalTrials.gov. A Phase II/III, Multicenter, Randomized, Placebo-controlled Study of Gemcitabine Plus Cisplatin With or Without M7824 (Bintrafusp Alfa) as First-line Treatment of Biliary Tract Cancer. https://clinicaltrials.gov/ct2/show/NCT04066491. NCT04066491. Accessed August 30, 2019.

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iary drains, with the latter being complex and requiring frequent maintenance.[19]

The Nursing Advisory Board of The Cholangiocarcinoma Foundation gathered discharge instructions on biliary drains at baseline from 10 university centers and developed a SurveyMonkey questionnaire based on this information.[19] The questionnaire was sent to the 27 leading cancer centers of the National Comprehensive Cancer Network.

Of the 26 centers that responded, 23 completed the entire survey. Results showed that at least 74% of the time, patient education was completed by a combination of registered nurses and nurse practitioners. Verbal and written instructions were provided by 87% of the cancer centers; 13% provided verbal instructions only.

These findings suggest that patient education is inconsistent with respect to all the questions asked. There were wide variations regarding the care of external biliary drains, and less variation regarding internal stent exchange. At least 95% of the cancer centers instructed patients on signs and symptoms they need to report (ie, fever, jaundice, chills, absence of drainage, nausea, and vomiting); these instructions were given predominantly by radiology nurses.

Physician perspectives

According to physicians, the most urgent need is the encouragement of clinical trial participation, which requires collaboration and patient advocacy to increase awareness, along with supportive care to convince patients to stay on study and to ensure that their needs are met. They expressed that the second most urgent need is routine tumor profiling, which can enhance the understanding of tumor heterogeneity, resistance, and sequencing and combinations of therapies.

They also identified innovation as another critical need. In the diagnosis of CCA, brushing is inadequate and results in delayed care. Fluorescence in situ hybridization and early use of liquid biopsy may hasten appropriate patient care. Proper sequencing of therapies also requires innovation. This was the case with chronic myeloid leukemia, which previously had dim prospects for survival but has now become a chronic disease because of the use of targeted therapies.

Physicians believe that big data and smart data are additional pressing needs for enhancing the treatment of rare cancers such as CCA. Komodo Health, for example, has an outcomes database that lets healthcare providers know where patients are receiving treatment, their access to therapies, and their treating clinicians.[20] Further development of artificial intelligence will allow for the identification of patterns that predict recurrence and response to treatment.

CHORUS DISCUSSION

The chorus of experts agreed that CCA incidence rates do not appear to be plateauing, which is alarming. Data suggest that the increasing rates of intrahepatic CCA may be related to concomitant increases in the prevalence of certain risk factors, such as cirrhosis, alcoholic liver disease, and hepatitis C virus infection. They noted that a specific risk factor for most patients with CCA, however, has yet to be identified.

One of the less commonly described modifiable risk factors for CCA is metabolic syndrome. Case-control and cohort studies show a correlation between body mass index and the risk for CCA, particularly intrahepatic CCA.[21,22]

The data reviewed at the summit showed that obese patients are developing intrahepatic CCA at a younger age, with onset 5 to 10 years earlier than nonobese patients. A much larger percentage of intrahepatic CCA cases than previously thought may be attributed to obesity. "I think this is an area in which we really need to pay a lot of attention, particularly given the increase in obesity rates, at least in North America," said one of the experts. Overall, the data presented highlight the interplay between genetic factors and the environment.

The audience was polled with respect to the question, *"Where should the research focus be for the role of obesity in CCA?"* More than one-third (38%) responded, "educational interventions for obese patients and their providers," whereas 26% answered "predictive biomarkers in obese patients" and 24% responded "risk reduction strategies in obese patients." A minority (12%) of the participants believed that CCA screening programs in obese patients should be the focus.

The role of systemic therapy in CCA continues to evolve in advanced biliary tract cancers, as does the treatment paradigm in general. Although the ABC-02 trial set the benchmark for a standard of care in this setting, no single chemotherapeutic agent or combination regimen thus far has consistently led to objective tumor shrinkage, forestalled the need for palliative interventions, or extended survival beyond approximately 1 year. The overall response rate in the ABC-02 trial was only 30% collectively.[23] Most participants were in favor of clinical trial enrollment in the CCA patient population, whenever possible.

Next-generation sequencing (NGS) is a wave of the future, given the multiple molecular alterations that have been characterized in patients with CCA. These molecular alterations can be targeted by specific inhibitors that have already been developed and are continuing to be developed.

The discussion on urgent clinical needs in CCA highlighted the fact that patients are already at the forefront of change by requesting more specialists, more education, and more aggressive, novel treatment approaches—even at the cost of high mortality and even if the likelihood of cure is remote. Patients are requesting more routine insurance coverage for innovative diagnostic and therapeutic techniques, routine access to molecular profiling, and routine participation in clinical trials, even if there is no guarantee that an investigational treatment will help and if high risks are involved.

It was agreed that biliary drainage is an important part of patient care, both in the palliative and therapeutic settings. Regarding biliary drainage, the audience was asked to consider the following case study:

A 61-year-old patient with a type 3A hilar CCA presents to the clinic. Symptoms include jaundice and mild pruritus, but the patient is otherwise well and is afebrile. The patient's body mass index is 36, and there is radiographic evidence of a fatty liver. Laboratory values are as follows: bilirubin, 5.4 mg/dL; alkaline phosphatase, 304 U/L; aspartate aminotransferase/alanine aminotransferase, 200s (U/L); white blood cell (WBC) count, 13.4 x 10^9/L. Which of these factors would lead you to opt for biliary drainage?

Almost half (48%) of the audience members responded that jaundice and pruritus would lead them to opt for biliary drainage, whereas 26% selected the bilirubin level. Overall, 17% of the participants indicated that the patient would require portal vein embolization to ensure adequate FLR volume. Additionally, 9% of the participants responded that the WBC count would matter most.

According to multiple chorus experts, the decision to stent may depend on whether the cancer is resectable. "If it's resectable, you want to do biliary decompression, but you are also going to need to do portal vein embolization," noted one expert. "However, if it is not resectable and the treatment is going to be chemotherapy…I do not think any oncologist will give chemotherapy with a bilirubin of 5.4 mg/dL. That is when the bilirubin in the context of other variables may also have an important effect on that decision."

Updates on Cholangiocarcinoma in 2019: What's Hot?

Milind Javle, MD, Professor, Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, provided an update on the latest findings in CCA. According to Dr Javle, ultrasound screening and early detection of CCA are possible in an endemic population. In a 5-year population-based study of 4225 Taiwanese adults aged 30 to 60 years, CCA was detected in 32 individuals, with 21 of the 32 cases resectable.[24] Two simple radiologic metrics—periductal fibrosis and biliary ductal dilation—correlated well with each other and with CCA.

These data suggest that preneoplastic lesions are detectable and may have implications for screening high-risk groups in Western populations, specifically those patients who have nonalcoholic steatohepatitis or PSC.

Molecular targeting

A transformation in the management of CCA has occurred with the advent of NGS and targeted therapeutics. "CCA is a model for precision medicine and oncology," noted Dr Javle.

A distinct pattern of mutations is observed in patients with intrahepatic CCA, with a predominance of isocitrate dehydrogenase (*IDH*), *FGFR*, and *BRAF* mutations.[25] Extrahepatic CCA has a high frequency of *ERBB2* mutations, as well as some *BRAF*, *EHCCA*, and *KRAS* mutations, whereas gallbladder cancer has a high frequency of *ERBB2* amplification.[26]

Unfortunately, only 50% to 60% of patients with intrahepatic CCA and <30% of patients with extrahepatic CCA have enough DNA extracted from tumor tissue for sequencing. The molecular landscape of CCA

Table FGFR inhibitors in *FGFR2* fusion–positive cholangiocarcinoma

	Infigratinib (BGJ398) N = 67	Pemigatinib (INCB0548282) N = 107	TAS 120 (FGFR Alteration) N = 28	Deranzanitinib (ARQ 087) N = 29	Erdafitinib (JNJ42756493) N = 7
Patient demographics	Prior lines of treatment: 1: 38% 2: 32% 3+: 30% Stage IV at enrollment: 96%	Prior lines of treatment: 1: 51% 2: 32% 3+: 17% Stage IV at enrollment: 66%	Prior lines of treatment: 1: 29% 2: 29% 3+: 42% Stage IV at enrollment: not reported	Prior lines of treatment: 1: 52% 2: 35% 3+: 13% Stage IV at enrollment: 62%	Prior lines of treatment: 1: 36% 2: 36% 3+: 27% Stage IV at enrollment: not reported
ORR	26.9% 2L patients: 39.3% 3L+ patients: 17.9%	36%	25.0%	20.7%	57.1%
DCR	83.5%	82%	78.6%	82.8%	100%
mPFS	6.8 mos	6.9 mos	Not reported	5.7 mos	5.6 mos (includes 4 non-fusion patients)
mOS	12.5 mos	15.8 mos	Not reported	Not reached	Not reported
Company	QED	Incyte	Taiho	Basilea/ArQule	Janssen

DCR indicates disease control rate; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate.

is accessible via circulating tumor DNA, which can be used to personalize treatment.

In clinical trials, patients with CCA containing *FGFR2* fusions had superior response rates to FGFR inhibitors than to chemotherapy in the second-line setting. A relatively small percentage of patients do not respond to FGFR inhibitors in the presence of *FGFR* fusions. The small-molecule tyrosine kinase inhibitors directed against *FGFR* fusions that are in development all induce a similar disease control rate (approximately 80%) with a similar progression-free survival (PFS) of approximately 6 months (**Table**).[27-31] In patients with CCA who have received 1 prior line of chemotherapy, the response rate to FGFR inhibitors seems to be higher compared with patients who have received ≥2 prior lines of chemotherapy.[27]

According to Dr Javle, "It is therefore imperative upon all of us that we investigate these agents earlier in the disease course, such as in first-line therapy, where response rates may be perhaps even higher."

The most common mechanism of resistance to FGFR inhibition was gatekeeper mutations in the adenosine triphosphate binding pocket.[32] Several secondary gatekeeper mutations can be detected both in the blood and in the tumor. These tumors can then be targeted by irreversible pan-FGFR inhibitors.

Recent results from the phase 3 ClarIDHy study showed the IDH1 inhibitor ivosidenib to be effective in patients with *IDH1*-mutant intrahepatic CCA—a mutation that occurs in approximately 15% of individuals with CCA.[33] Although to date, personalized therapy has focused on mutational targeting, much information exists beyond the mutations, including data on RNA and organoids.

Immunotherapy

Trials of the immunotherapeutic agent pembrolizumab with or without granulocyte-macrophage colony-stimulating factor in patients with advanced biliary tract cancer have reported modest response rates.[34] Therefore, the use of standard single-agent checkpoint inhibitor therapy may not be the ideal solution for patients with this disease, who may instead require combination regimens.

Adjuvant therapy

Until recently, no standard adjuvant therapy had been available for the treatment of patients with CCA. The BILCAP adjuvant therapy trial demonstrated numerical superiority of adjuvant capecitabine versus observation, although it did not reach statistical significance.[35] A protocol-specified sensitivity analysis, adjusting for relevant prognostic factors, showed a significant approximately 30% improvement in overall survival

with adjuvant capecitabine, which has become the standard of care following surgical resection.[35]

Ablative radiotherapy

The use of ablative radiotherapy has not been evaluated in randomized phase 3 studies. Instead, large-volume institutions and real-world studies serve as the basis of information on the utilization of this treatment. If the underlying liver function in a patient with intrahepatic or extrahepatic CCA is good, then the liver can withstand large doses of radiation. In a retrospective, dose-response analysis of 79 patients with inoperable intrahepatic CCA who received radiation doses of 35 to 100 Gy (median biologic equivalent dose, 80.5 Gy), PFS and overall survival reached a plateau with a median follow-up of 33 months, indicating that a subgroup of patients benefit from radiation following systemic chemotherapy.[17]

Recent advances in the treatment of CCA are explored in greater detail in subsequent articles in this publication. ■

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Medical Management of Patients with Advanced Cholangiocarcinoma

Advances in Chemotherapy for Cholangiocarcinoma

According to several presenters at the First Annual Cholangiocarcinoma Summit, advances in systemic treatment for cholangiocarcinoma (CCA) are emerging, including cytotoxic chemotherapy. Earlier this year, the combination of gemcitabine, cisplatin, and nab-paclitaxel was investigated as first-line therapy in 60 patients with advanced CCA and gallbladder cancer with good performance status.[1] Among evaluable patients, the median progression-free survival (PFS) was 11.8 months, the median overall survival (OS) was 19.2 months, and the partial response rate was 45%. Overall, 20% of the patients converted from unresectable to resectable disease and underwent curative surgery.[1]

The randomized, phase 3 Southwest Oncology Group: S1815 clinical trial evaluated the combination of gemcitabine, cisplatin, and nab-paclitaxel versus the gold standard of gemcitabine plus cisplatin in patients with newly diagnosed, advanced biliary tract cancers.[2] Archived diagnostic tissue is being banked and serial blood is being collected, including at the time of disease progression. This study represents the largest repository of biliary cancer specimens to date, and a translational plan is being developed for biospecimens.

The randomized, multicenter, phase 3 NuTide 21 trial is comparing NUC-1031 (a nucleoside analogue similar to gemcitabine) plus cisplatin versus gemcitabine plus cisplatin) in patients with previously untreated locally advanced or metastatic biliary tract cancer.[3] The primary objectives of this study are OS and objective response rate. Several other studies are assessing targeted therapies in cytotoxic combination settings.

These studies are all collaborative efforts, which will continue to be instrumental to investigate the replacement of the current chemotherapy standard of care and the utility of chemo-intensification, as well as the use of chemotherapy in combination with targeted therapies and immunotherapy, noted one presenter. Since immunotherapy and targeted agents are not suitable for all patients, new chemotherapeutic agents in both first- and second-line settings are still needed.

Multiple chemotherapy options exist when first-line chemotherapy (gemcitabine plus cisplatin) has failed. The scenario is challenging with respect to second-line chemotherapy for patients with CCA, in part because the aggressive behavior of the disease renders few patients sufficiently fit to receive second-line chemotherapy following progression on first-line therapy.

Most trials of second-line chemotherapy for CCA have been phase 2 studies (none of which were randomized) and retrospective analyses. Response rates in these trials were <10% overall, with a modest benefit in PFS and OS.[4]

ABC-06 was a phase 3, randomized, open-label clinical trial that assessed the role of FOLFOX (folinic acid [leucovorin], 5-fluorouracil [5-FU], and oxaliplatin) plus active symptom control (ie, control of complications related to the cancer, as well as to biliary obstruction) versus active symptom control alone in the second-line setting in patients diagnosed with biliary tract cancer, including ampullary tumors.[5]

FOLFOX improved OS (the primary end point) on an intent-to-treat basis after progression following gemcitabine plus cisplatin with a clinically meaningful reduction in the risk for death (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.50-0.97; P = .031). The rate of OS in the FOLFOX arm was increased by an absolute 15.1% at 6 months (50.6% vs 35.5% in the active-symptom-control-alone arm) and by 14.5% at 12 months (25.9% vs 11.4%, respectively).[5]

Subgroups with a poorer prognosis seemed to benefit the most from FOLFOX, including patients who were platinum resistant or refractory, those with low levels of albumin, and those with metastatic disease. Based on these data, FOLFOX plus active symptom control became the new standard of care in the second-line setting for advanced biliary tract cancer.[5]

In a phase 2 trial in the second-line setting, treatment with FOLFIRINOX (leucovorin, 5-FU, irinotecan, and oxaliplatin) resulted in a PFS of 6.2 months.[6] Etoposide toniribate, a prodrug of etoposide, demonstrated evidence of activity compared with best supportive care in a small (N = 22) phase 2 study, with disease control rates of 55.6% versus 20.0%, respectively.[7]

Predictive Molecular Biomarkers in Cholangiocarcinoma

The International Cancer Genome Consortium has analyzed 500 cases of CCA from 10 countries and has identified 4 distinct clusters with different clinical features and molecular profiles.[8] The clusters do not necessarily match the anatomic location, although the 2 are correlated. Among the 4 clusters, tumors in cluster 4 are associated with the best outcomes. Patients with

tumors in cluster 4 present predominantly with intrahepatic CCA enriched by *IDH1* mutations and *FGFR* alterations. In contrast, tumors in cluster 1 are associated with the worst outcomes. Patients with tumors in this cluster have *TP53* mutations, *BRCA1/2* mutations, and *HER2* amplification.[8]

Comprehensive genomic profiling from >1000 patients in the FIGHT-202 trial confirm findings from The Cancer Genome Atlas (TCGA) that few CCA tumors are microsatellite instability (MSI)-high or have high tumor mutational burden.[9] In the TCGA, *IDH1* mutations and *FGFR2* alterations were found in 10.5% and 9.4% of patients with CCA, respectively.[9]

FGFR alterations are associated with a unique epidemiology and, perhaps, natural history. These alterations usually present in younger patients, at an earlier stage, and have an indolent disease course. *IDH1* mutations are also pursued in the treatment of CCA in the second-line setting. *IDH1* remains a very rare mutation in gastrointestinal cancers and is specific to CCA. It is comutated with *ARID1A*, *BAP1*, and *PBRM1*.

BRAF mutation seems to be a promising targetable alteration in CCA. In the ROAR basket trial, in which 17% of the patients had hepatocholangiocarcinoma,[10] combination therapy with dabrafenib plus trametinib was associated with a 42% overall response rate (ORR), a median PFS of 9.2 months, and a median OS of 11.7 months in *BRAF*-mutated patients with CCA.[11]

Tumor location seems to be a predictive biomarker for targetable mutations. When faced with a carcinoma of unknown primary origin, the diagnosis must be confirmed and attributed appropriately, ensuring that the tumors are not metastatic, stated one of the participants. Documenting the location of CCA tumors—that is, intrahepatic versus extrahepatic—is necessary. Patients with intrahepatic CCA have a high likelihood of targetable genomic alterations and should undergo tumor genetic testing in a timely fashion.

Tumors are genomically unstable, and the potential for evolution is a real phenomenon in attempting to capture molecular markers. "If you look at the primary tumor from 5 years before the patient received a couple of lines of therapy, are we looking at the tumor that now threatens the patient's life?" asked one presenter.

The methodology selected for tissue acquisition in patients with CCA is important. Core needle biopsy is preferred, because it supplies more tissue for analysis and provides details about the stroma, lymphocytic infiltrate, and angiogenesis to assist in the patient's diagnosis. In many cases, aspiration is preferred, to avoid tumor spread at the time the material is acquired.

The methodology for liquid biopsy is improving rapidly, with many assays now being used in the marketplace. The expectation is that as liquid biopsy assays improve and can detect more types of abnormalities, they will become more widely used. For many oncologists, liquid biopsy is the first choice for patients with disease recurrence, because the results are returned quickly and the coverage is relatively broad (ie, a large number of genes) in many of the assays that are available. The expectation among the experts at the meeting was that the use of liquid biopsy will expand rapidly, particularly at various points in the decision-making process, as the assays improve.

CHORUS DISCUSSION

The chorus members were asked how they would use gemcitabine and cisplatin off clinical trial. Nearly half (46%) indicated that they would treat until progression, 26% responded that they would treat for 6 months and

then stop chemotherapy until progression, 23% said that they would treat for 6 months and then stop cisplatin while continuing gemcitabine maintenance, and 5% responded "other."

When they were asked to characterize their current use of liquid biopsies, 32% said that they obtain a liquid biopsy only if the tissue is of insufficient quantity for next-generation sequencing (NGS), 23% responded that they do not use liquid biopsies, 19% answered that they obtain a liquid biopsy from all patients at baseline and at progression, 10% indicated that they obtain a liquid biopsy in biomarker-positive patients at baseline and at progression, and 3% noted that they obtain a liquid biopsy in all patients at baseline only.

Molecularly Targeted Therapies

FGFR inhibitors

Activation of the FGFR pathway has been shown to be a favorable prognostic factor in intrahepatic CCA. Alterations in *FGFR* have been associated with improved OS compared with wild-type *FGFR*. FGFR-specific inhibitors have been found to contribute to improved OS compared with the use of standard therapies in this setting.

The most described genetic abnormality in CCA is *FGFR* fusion, in which the *FGFR* gene fuses with another gene. In this regard, up to 50 gene fusion partners have been recognized. Several selective and nonselective FGFR inhibitors are in development.

In patients with *FGFR2* fusion–positive CCA, the ORR to infigratinib is 31%, with a disease control rate of 84%.[12] Across the various FGFR inhibitors, the number of lines of prior therapy seems to have an impact on response rates. The belief among presenters at the summit is that NGS will eventually be used for treatment decisions in this setting, and FGFR inhibitors may be used first line with identification of *FGFR* fusions.

An overrepresentation of *FGFR* genetic abnormalities has been observed among patients with locally advanced intrahepatic CCA who are candidates for transplantation. These patients tend to have impressive survival following transplant, so *FGFR* abnormalities may have implications in terms of patient selection for transplantation.

Resistance to FGFR inhibitors

Primary resistance to FGFR inhibitors can occur because of tumor heterogeneity, other tumor-related factors, or drug-related issues. Tumor-related factors include incomplete addiction to FGFR and comutated pathways or other upregulated bypass pathways for which FGFR inhibition alone is insufficient for a response. Although *FGFR2* fusion appears to be an early alteration, other factors may have an impact on the sensitivity of CCA tumor cells to FGFR inhibitors, some of which may be heterogeneous across cells.

Comutations with *FGFR2* fusion may affect the sensitivity of CCA to FGFR inhibitors. In a recent analysis, patients with an *FGFR2* fusion and a *TP53* alteration had no response to pemigatinib. Moreover, the response to pemigatinib in patients with *CDKN2A/B* alterations was decreased compared with that in the entire *FGFR2*-positive population.[13]

An integrative molecular analysis of cell-free (cf) DNA, primary tumors, and metastases was conducted in 3 patients with advanced *FGFR2* fusion–positive intrahepatic CCA. Results of the study revealed the emergence of secondary kinase mutations that confer resistance to infigratinib at the time of progression, in addition to a striking degree of interlesional heterogeneity, with distinct *FGFR2* point mutations identified in different metastases from the same patient.[14]

The highly selective, covalent-binding pan-FGFR inhibitor TAS-120 may overcome resistance to ATP-competitive FGFR inhibitors, as evidenced by studies in biliary tract cell lines and in patients with intrahepatic CCA. TAS-120 was found to be active against 4 *FGFR2* mutations but had relatively less activity against the *V565F* gatekeeper mutation.[15]

"My practice is such that when I have a patient on an FGFR inhibitor, we do serial cfDNA analysis. We never stop the drug based just on the emergence of resistance. We always wait until we see progression on a scan," said an audience member. The emergence of certain resistance mutations would prompt switching to an alternate FGFR inhibitor, such as Debio 1347 (a highly selective FGFR1, 2, 3 ATP competitive inhibitor) or TAS-120, because prior FGFR inhibitor treatment usually precludes enrollment in a clinical trial with these agents.

IDH1 inhibitors

IDH mutations occur in up to 23% of patients with CCA, and in contrast to other targetable mutations, they do not play a prognostic role in CCA.[16,17]

The phase 3 ClarIDHy study was a randomized, double-blind, international study of adults with histologically confirmed CCA and centrally confirmed mutated *IDH1* by NGS who had received 1 or 2 prior lines of therapy.[18] Patients were randomized in a 2:1 fashion to ivosidenib 500 mg administered once daily or placebo. Crossover was permitted at radiographic disease progression.[18]

Median PFS was 2.7 months in the ivosidenib group versus 1.4 months in the placebo arm (HR, 0.37; 95% CI, 0.25-0.54; P <.001).[18] In the ivosidenib treatment arm, PFS was 32% at 6 months and 22% at 12 months, which is impressive when considering that the OS in this late-line setting is typically measured on the order

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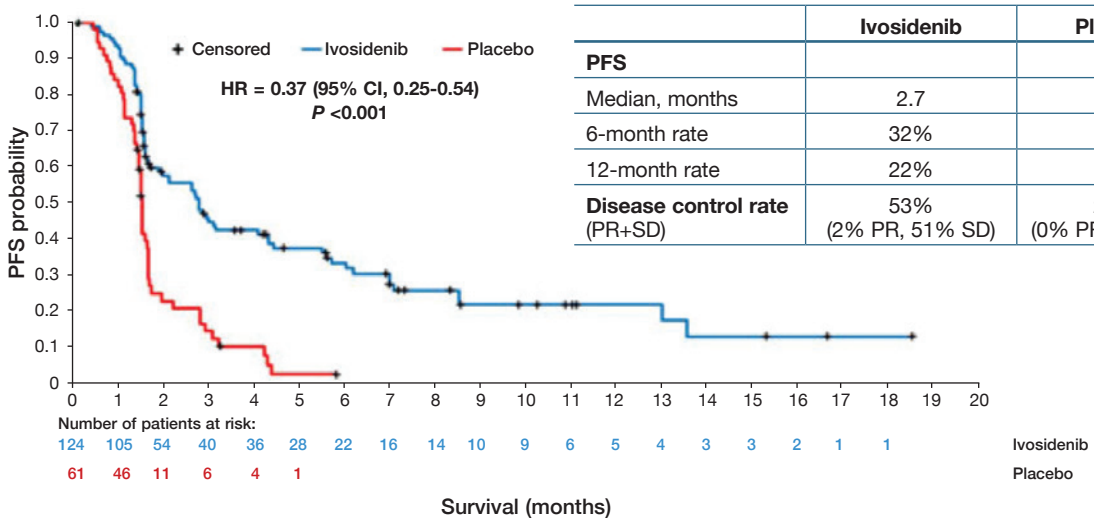
Figure 1 Progression-free survival in the ClarIDHy trial.



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

CI indicates confidence interval; HR, hazard ratio; NE, not evaluable; PFS, progression-free survival; PR, partial response; SD, stable disease.

of a few months (**Figure 1**).[18] These values were not evaluable in the placebo arm because of crossover. Treatment with ivosidenib was associated with a greater disease control rate of 53%, including 2 confirmed partial responses, compared with placebo recipients, in whom stable disease was documented in only 28%.[19]

Median OS was numerically longer with ivosidenib than with placebo (10.8 vs 9.7 months, respectively).[18] OS rates at 6 and 12 months were 67% and 48%, respectively, in the ivosidenib group, compared with 59% and 38%, respectively, in the placebo group.[19]

The investigators used a rank-preserving structural failure time method to reconstruct the survival curve for the placebo arm, as if they had never crossed over to ivosidenib. When used, the OS for the placebo group was 6 months, which is consistent with the survival data in the active symptom control arm from the ABC-06 study.[5] The median OS became statistically significant with a *P* value <.001.[18]

These data demonstrate the clinical relevance and benefit of ivosidenib in *IDH1*-mutated CCA and establish the role of genomic testing in this rare cancer with a high unmet need. The consensus among the participants at the summit was that the results from ClarIDHy will mandate molecular profiling of all patients with CCA.

Other Emerging Molecular Targets

The spectrum of targets in both intrahepatic and extrahepatic CCA is large and includes drugs already in the advanced stages of clinical testing. Emerging molecular targets for CCA include the mitogen-activated protein (MAP) kinase and human epidermal growth factor receptor 2 (HER2) pathways.[20,21]

The rationale behind targeting MAP kinase is that mutations in *BRAF* are frequently associated with enhanced sensitivity to MEK inhibition and may constitute a survival mechanism for mutated cells. The MAP kinase pathway appears to be active in 75% of biliary cancers.[22] In vivo and in vitro data demonstrate that MEK inhibition suppresses tumor growth in patients with CCA. Expression profiling across a panel of 7 human biliary cancer cell lines showed several RAS/MAP kinase pathway components and demonstrated sensitivity to MEK inhibitors.

Selumetinib and binimetinib are oral inhibitors of MEK1/2. A small phase 2 study of selumetinib in patients with advanced biliary tract cancer reported a 12% objective response rate, with 1 patient achieving a complete response (CR).[23] Among 28 patients treated with binimetinib, 1 CR and 1 partial response (PR) were recorded. Overall, 43% (12 of 28) of the patients had stable disease.[24]

Mutations in *BRAF* have been found in about 5% of biliary tract tumors and may be enriched in intrahepatic biliary tract cancers.[25] ROAR was a phase 2 open-label multicenter basket study of the combination of dabrafenib plus trametinib in patients with *BRAF* V600E-mutated cancers.[11] In the evaluable/intent-to-treat population, median PFS was 9.2 months and median OS was 11.7 months, suggesting that this MEK/BRAF inhibitor combination is a promising treatment option for this patient population.

Aberrant activation of the RAS/RAF/MAPK pathway occurs in >60% of biliary tract cancers.[26] Given the pivotal role of vascular endothelial growth factor, the RAS/RAF/MAPK pathway, and platelet-derived growth factor receptor-beta in the biology of biliary tract cancers, evaluation of tyrosine kinase inhibitors (TKIs) in the second-line setting represents a rational approach to treatment.

Regorafenib has been evaluated as second-line therapy in several studies of patients with CCA.[27-29] Modest ORRs of 9% to 11% were achieved, with a disease control rate of 56% to 70%, a median PFS as high as 15.6 weeks, a median OS as high as 31.8 weeks, and an 18-month OS as high as 35%.[27-29] With regorafenib plus gemcitabine/oxaliplatin combination therapy, improvements were reported with ORRs of 40%, median PFS of 11 months, and median OS of 28+ months.[27-29]

Abnormal HER2 activation is known to result in tumor growth. In patients with gallbladder cancer, *HER2* mutation/amplification has a prevalence rate of approximately 14%, which decreases to 5% to 7% in patients with CCA.[30]

Unlike in breast cancer, however, HER2-directed therapy has not become a standard of care in gallbladder cancer because of the absence of clinical trials performed in this small patient population.

The effects of neratinib (a pan-HER TKI) alone or in combination with paclitaxel or trastuzumab have been evaluated in patients with a variety of *HER2*-mutant tumors, including a cohort of 20 patients with biliary tract cancers (9 with CCA, 9 with gallbladder cancer, and 2 with ampullary cancer).[31] In this small subset of patients, 2 objective responses, both of which were PRs, were reported. The clinical benefit rate attributed to the treatment was 30%.[31]

"Looking at comutations, as was described with FGFR inhibitors, is equally important with targeted therapies," noted an audience member. "To make treatment more successful, we'll probably need combination therapies, because there is a low percentage of responses with monotherapy and the responses are not durable."

Using tissue NGS and blood cfDNA, several simultaneous molecular alterations have been discovered with *IDH1* mutations in CCA, many of which are potentially targetable for cancer therapies. These comutations may help to elucidate some of the resistance to IDH1 inhibitors.

Although alterations in DNA damage response (DDR) pathways are not highly prevalent in *IDH1*-mutant cancers, when they do exist, they may be targets for poly (adenosine diphosphate [ADP]-ribose) polymerase or ataxia telangiectasia and Rad3-related inhibitors. A relatively large representation of alterations involves activating the cell cycle, which may be targeted in combinations that include CDK4/6 inhibitors. In addition, PI3K activation through the *PIK3CA* mutation is observed with *IDH1* mutations, which potentially may be targeted with the addition of the PI3K inhibitors. Activation of the MAPK pathway, either through *BRAF* mutation or *K/NRAS* mutation, is a potential target for MEK inhibition with or without BRAF inhibition.

Some chemotherapeutic agents may exhibit an effect that can be targeted. For example, FF-10502-01, which blocks DNA synthesis, is a novel pyrimidine nucleoside analogue of gemcitabine that is currently in development. The agent exerts cytotoxic activity by inhibiting DNA polymerase alpha during DNA synthesis. FF-10502-01 can be incorporated by DNA repair polymerase beta and translesional synthesis polymerases (eg, *POLK*), and can thus terminate DNA synthesis during DDR. Its efficacy in patients with heavily pretreated CCA, in which all participants received prior gemcitabine, was evaluated in a phase 2 expansion of a phase 1 study, with an ORR of 11%. Responses with FF-10502-01 have lasted for as long as 12 months.[32]

Adverse Events Associated with Targeted Therapies

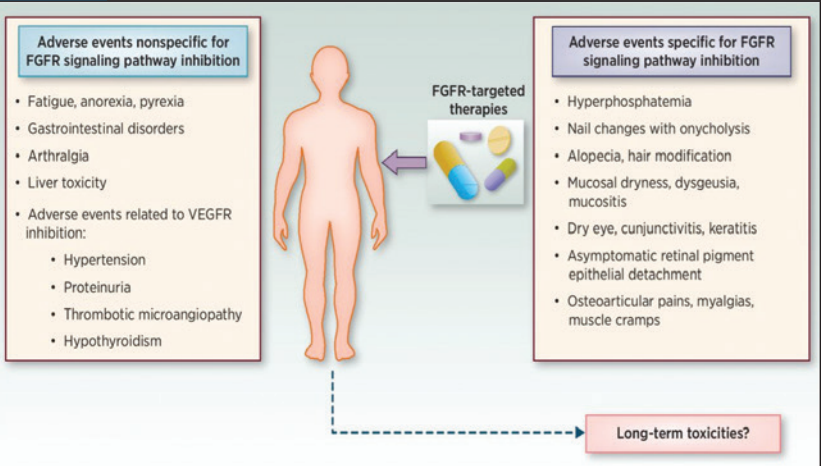
Newer targeted therapies have been reported to be safe and well tolerated. The toxicity profiles of these agents are clearly less burdensome than those associated with platinum-based chemotherapy. Given the chronicity of therapy with targeted agents, however, low-grade toxicities do matter and may necessitate intervention.

FGFR inhibition

Unique toxicities associated with FGFR inhibitors as a class include hyperphosphatemia, fatigue, stomatitis, alopecia, decreased appetite, dry skin, dry mouth, and nail toxicity (**Figure 2**).[33] Although most of the toxicities are grade 1 or 2, overall, 63.2% of the patients receiving infigratinib therapy require dose reduction and 77% require dose interruption. Nail toxicities also result in dose delay.[34]

Hyperphosphatemia can occur with the use of FGFR inhibitors, and its mechanism is not well understood. It is thought that the FGF ligand FGF23, which is secreted by the osteocytes, is responsible for phosphate and vitamin D homeostasis. Management of hyperphosphatemia requires dose adjustment or interruption in 42.6% of patients, along with additional medication and an intermittent dosing strategy.[35] Diet must be modified to eliminate foods high in phosphates[35] (ie, dairy, meat, nuts, processed food). With grade 3 hyperphosphatemia, the dose of FGFR inhibitor should be reduced and phosphate levels should be rechecked frequently. With

Figure 2 Common adverse events associated with FGFR inhibitors.



FGFR indicates fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

grade 4 hyperphosphatemia, the dose of FGFR should be interrupted and resumed at a lower dose once the toxicity level is less than grade 2.

Although the presence of ocular toxicity with FGFR inhibition is uncommon, it is serious in nature. The rate of serous retinal detachment observed in the phase 2 study with pemigatinib was 4%.[36,37] An ophthalmologic evaluation is required at baseline, again 4 to 6 weeks after initiating the FGFR inhibitor, and then as needed. For dry eye, artificial tears or lubricant at night may be necessary.

Skin toxicity is also an issue with FGFR inhibitors, with hand–foot syndrome and nail toxicity being the most bothersome. Nail toxicity can be functionally limiting and may require dose modification.

IDH inhibition

The experience with ivosidenib in clinical trials is that the agent is well tolerated, with fatigue, nausea, and other gastrointestinal side effects being the most frequently reported treatment-emergent adverse events (TEAEs). The most common TEAEs in the phase 3 study were ascites, an increase in bilirubin levels, anemia, and an increase in aspartate aminotransferase levels. TEAEs leading to treatment discontinuation were more common with placebo than with ivosidenib.[38]

Because ivosidenib is a cytochrome P450 (CYP450) inhibitor, hepatic impairment is a possible TEAE. If the agent is coadministered with a strong CYP3A4 inducer, the dose of ivosidenib should be reduced by 50%. A high-fat meal should not be administered with ivosidenib, as it can increase concentrations of the drug.

QTc prolongation with ivosidenib may be an issue in patients who are taking other medications that are known to cause QTc prolongation. An electrocardiogram performed weekly for the first 3 weeks after initiating ivosidenib and monthly thereafter is recommended.

CHORUS DISCUSSION

The landscape of CCA treatment will be changed permanently with the introduction of FGFR and IDH inhibitors, and molecular profiling will become standard, hopefully at diagnosis, the chorus members agreed. Consensus was also reached regarding the increased use of liquid biopsy, which will complement tissue-based testing.

According to the participants, the use of cfDNA outside of clinical trials, for the purpose of data collection and treatment decisions, should not yet be routine. Although the utilization of cfDNA as a research tool that is intended to create more effective therapies is valuable, the clinical decision would probably not be affected until further research validates this use. Additionally, the extra cost incurred with the use of cfDNA cannot be justified at this time. Some of the mutations identified are subclonal and may not be leading to treatment resistance, stated one of the participants. Because the genetic profile of a tumor changes >60% of the time in a patient receiving targeted therapy, one scenario in which the use of cfDNA might be indicated in clinical practice is the patient who is receiving targeted therapy and has a good overall prognosis, the presenter argued.

Since targeted therapies are here to stay, the management of toxicities associated with these treatments needs to move forward and involve other disciplines, such as dietitians, ophthalmologists, and dermatologists, among others, the participants agreed. The involvement of these other disciplines may be more challenging in the community or even in mid-level hospital centers, however, where many patients are treated. In the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) trial,[39] for example, the response rate to immunotherapy among patients with MSI-high cancers correlated with toxicities, as therapy was being discontinued in patients who were experiencing toxicity because of the lack of availability of a nephrologist or a hepatologist for referral. Even when available, community dermatologists may not be comfortable managing the symptoms associated with targeted therapies (eg, nail toxicity) and immunotherapies.

"As more targeted therapies become available, it is going to be important to educate our primary colleagues…our subspecialty colleagues…because it's a team-based effort," noted one of the chorus members.

"One of the things that will be critical for patients receiving FGFR inhibitors is to make sure that the side effects are managed appropriately [in phase 3 clinical trials and at large institutions involved], so that people don't discontinue experimental therapy prematurely," noted another participant.

Immunotherapy: The New Frontier?

The tumor microenvironment creates obstacles and opportunities for the use of immunotherapy. Hot tumors are MSI-high, containing many immune infiltrates and cytotoxic T-cells. Cold tumors have a dearth of immunosuppressive cells. Biliary tract tumors are considered cold, since they are populated with myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory T-cells, with an absence of cytotoxic T-cells and natural killer cells.

Programmed death-ligand 1 (PD-L1) expression is an elusive biomarker, because no correlation has been demonstrated between PD-L1 expression and response to immunotherapy across different types of cancer. The tumor versus stromal component of PD-L1 expression is one caveat to quantifying PD-L1 expression and the stain used to identify PD-L1 positivity is another. A third caveat is the level of PD-L1 expression that is used to define a PD-L1–positive tumor.

The KEYNOTE-028 and KEYNOTE-158 trials of pembrolizumab in patients with biliary tract cancer demonstrated modest ORRs of 13.0% and 5.8%, respectively.[40] Whereas KEYNOTE-028 enrolled PD-L1–positive patients, KEYNOTE-158 was a trial of patients who were not selected on the basis of PD-L1 expression. Given low response rates, single-agent checkpoint inhibition would appear to offer little advantage at a high cost in patients with biliary tract cancer.

In a phase 1 study of patients with biliary tract cancer, dual therapy with durvalumab and tremelimumab was associated with a median OS of 10.1 months.[41] The rate of TEAEs with combination therapy was 82%, with grade ≥3 TEAEs reported in 23% of these patients.[41] The use of chemotherapy may enhance the effect of immunotherapy by causing immunogenic presentation of antigens or tolerance through cell death, whether apoptotic, autophagic, or necrotic.

To capture patients before the end stages of their disease, 3 ongoing studies (Bilt-01, Bilt-02, and Bilt-03) are exploring the use of immunotherapy in earlier settings in biliary tract cancer. Moreover, efforts to optimize the tumor–stromal interaction include the use of a colony-stimulating factor-1 receptor antibody, which recruits myeloid cells to the tumor microenvironment, stabilizes the number of tumor-associated macrophages, and suppresses tumor immunity.

Another combination approach uses transforming growth factor (TGF)-beta bispecific inhibition combined with anti–PD-L1 antibody. M7824 is a bispecific monoclonal antibody that sequesters TGF-beta and inhibits PD-L1 expression. The initial clinical trial of this combination therapy was evaluated in 30 patients with biliary tract cancer and generated an overall response rate of 20%.[42] More impressive is the fact that the median duration of response was not reached, and the median OS was 12.7 months.[42]

Granulocyte-macrophage colony-stimulating factor, a cytokine growth factor that may promote CD8-positive T-cell infiltration into tumors and tumor antigen-specific T-cell expansion, has been studied in combination with pembrolizumab in pretreated patients, inducing an ORR of 19% and a median OS that has not yet been reached.[43]

MEK inhibition in combination with an anti–PD-L1 antibody is being investigated in a trial of patients with unresectable CCA. Paired core tumor biopsies are a key component of this study, in which changes in immune cell subsets and markers of immune exhaustion will be assessed in MEK-inhibitor–treated versus non-MEK inhibitor–treated CCA patient samples.

Whereas MEK inhibition in only the tumor can stop uninhibited tumor cell growth, whole body MEK inhibition is problematic because it may have both positive and negative effects on the immune system. An MEK inhibitor may cause changes in the tumor cells that render them more visible to the immune system and thus easier to attack. MEK inhibitors may have a direct negative impact on immune cells, however, specifically impairing the activation of T-cells.

Histone deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors are epigenetic modulators with immunomodulatory potential in patients with CCA. They function with respect to posttranslational modifications of chromatin and work in concert to determine whether a given gene is expressed. Both HDAC inhibitors and DNA methyltransferase inhibitors can upregulate many features to elicit an immune response. They increase major histocompatibility complex class expression, cytotoxic T-cell infiltration, and costimulatory molecule expression, while decreasing the expression of immunosuppressive cells. ■

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Surgery for Cholangiocarcinoma: Before and After

At the First Annual Cholangiocarcinoma Summit, presenters discussed recent advances in the management of patients with cholangiocarcinoma (CCA), including new surgical approaches, the expanding role of liver-directed therapies, radiation, and transplantation, and more effective sequencing of neoadjuvant and adjuvant therapies.

Surgery

Hilar cholangiocarcinoma

Surgery for hilar CCA, or Klatskin tumor, is dependent on the extent of the disease. The Bismuth Corlette classification considers the spread of the tumor in one dimension, along the biliary tree, and is based on the extent of ductal infiltration. Typically, tumors in the Bismuth I stage are considered resectable. Tumors at stage IV were traditionally thought to be unresectable, as they had spread to the bilateral second-order biliary radicals.

The goal of resection in patients with hilar CCA is a margin-negative resection, leaving at least 2 contiguous liver segments with adequate perfusion and biliary drainage. The surgery typically starts with a diagnostic laparoscopy, followed by a portal lymphadenectomy for staging, and then the removal of the bile duct, involved liver, and the caudate lobe, depending on the tumor location. A portal vein resection is then performed, if necessary, followed by reconstruction. Diagnostic laparoscopy is a critical aspect of the procedure, as it may identify disease features not detected on imaging.

The Blumgart preoperative clinical T-staging system for hilar CCA, which was devised to determine resectability, is defined by the radial and longitudinal extent of a tumor. In a series of 380 patients at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City, fewer than half of all individuals who were staged underwent curative resection.[1] Most of these patients were found to be inoperable or with advanced disease. The median overall survival (OS) was 39 months, with a 5-year survival rate of 37.5%.[1] Patients who underwent a margin-positive resection had similarly poor survival to those who were not resected.

Intrahepatic cholangiocarcinoma

In patients with intrahepatic CCA, the goals of resection are the same as with surgery for hilar CCA. The procedure begins with a diagnostic laparoscopy, followed by a portal lymphadenectomy, which is a new paradigm shift, as this was not performed routinely as recently as a few years ago. Typically, a biliary resection is not necessary unless the tumor involves the hilum.

Despite curative treatment, approximately 60% of patients with intrahepatic CCA will experience recurrence, typically at a median of 2 years.[2] Most recurrences occur within the liver, which raises the question of whether patients with a margin-negative resection should receive adjuvant therapy or liver-directed therapy.

Distal cholangiocarcinoma

Surgery for distal CCA is similar to that of the Whipple procedure for patients with pancreatic cancer. The liver is not involved in this surgery. The major morbidity in distal CCA is associated with pancreatic reconstruction.

Minimally invasive surgery

Minimally invasive liver resection has lagged behind minimally invasive surgery for other indications because of the technical difficulty involved, the potential for significant blood loss, the complexity of the case, the reconstruction that is most often required, and the lack of dedicated training programs at most academic institutions. Over the past decade, however, implementation of the minimally invasive approach for hepatobiliary resections has been increasing.

Some of the factors that have allowed for adoption of this surgery include the introduction of endoscopic mechanical staplers, the Cavitron ultrasonic surgical aspirator, the TissueLink dissecting sealer, and the effect of pneumoperitoneum combined with low central venous pressure, which has limited blood loss and has improved patient outcomes.[3]

Comparative clinical trials of minimally invasive liver surgery and open surgery include the following:

- A double-blind, randomized trial of laparoscopic versus open left lateral sectionectomy plus an enhanced recovery program showed no differences between the 2 procedures with respect to length of hospital stay, overall morbidity/mortality, and hospital readmission rates at an interim analysis[4]
- In a comparison of minimally invasive (laparoscopic) surgery versus an open approach of parenchyma-sparing hepatectomy (ie, <3 segments), the minimally invasive approach was associated with a shorter length of hospital stay, thus resulting in a more cost-effective method[5]

- Another trial compared laparoscopic with open hepatectomy in patients with Child's A cirrhosis and a solitary tumor of <5 cm. The minimally invasive treatment arm experienced a significantly shorter operative time and shorter duration of hospital stay (P <.001 for both). The secondary outcomes of blood loss, complications/readmission rates, 30-day mortality rates, and recurrence rates were similar with both approaches.[6]

Perihilar cholangiocarcinoma

In patients with perihilar CCA, the challenges associated with the use of minimally invasive surgery involve the fact that the procedure is considered highly demanding because of the proximity of these tumors to the portal vein and hepatic artery. The caudate lobectomy is also technically challenging. Morbidity and mortality are high compared with those related to other modalities of hepatobiliary resections. The extremely difficult nature of the procedure and the fear of oncologic inefficiency have thus far limited the adoption of the minimally invasive surgical approach for the treatment of perihilar CCA.

The use of minimally invasive surgery in patients with perihilar CCA has not been well studied. A systematic review of 21 studies, with the largest series including 44 patients, reported a conversion rate to open surgery of 4.9% (7 of 142).[7] The average length of hospital stay across all the studies was 10.8 days (range, 3-58 days).[7] On pooled analysis, the rate of postoperative morbidity was 23.8% and the mortality rate at 90 days was 3.2%, which are far lower than the rates reported for open procedures.[7] Negative resection margin (R0) was attained in almost 80% of the patients. Limitations of this systematic review include the fact that 6 of the studies did not report follow-up after hospital discharge and the possibility of selection bias.[7]

Oncologic outcomes

The National Cancer Database was used to examine oncologic outcomes among 2309 patients with intrahepatic CCA who underwent 1997 open versus 312 laparoscopic hepatic resections between 2010 and 2015.[8] Nodal evaluation, which was performed in 58% of all patients evaluated, was significantly more common among patients who underwent open versus minimally invasive surgery (61% vs 39%, respectively; P <.001).[8] Adjuvant chemotherapy and radiation was used more frequently in patients who had ≥1 lymph nodes evaluated.[8] Based on these findings, it appears that an inability to establish nodal staging is associated with an inaccurate prognosis and thus can influence the use of adjuvant therapy in patients with intrahepatic CCA.

Liver-Directed Therapies

Surgical resection is the only curative option for intrahepatic CCA, but most patients are not candidates for this procedure. In addition, most patients die of intrahepatic tumor–related complications. The use of liver-directed therapies to control intrahepatic progression and thus improve survival may be appropriate for some patients.

A multitude of liver-directed therapies, including different forms of ablation, embolization technologies, and hepatic artery chemoperfusion, is available. However, no prospective, randomized trials of liver-directed therapies are available, and retrospective studies to date have enrolled small numbers of patients and a heterogeneous patient population.

Liver-directed therapies can be used in patients with both resectable and unresectable metastatic disease. Ablation technologies include radiofrequency ablation and microwave ablation (MWA).

Ablation

Ablation has been compared with resection in 2 studies of patients with recurrent intrahepatic CCA. In a comparison of MWA and surgical resection, no difference in 5-year OS was observed between the groups, but the group undergoing surgery had a longer procedure time, a longer length of hospital stay, greater blood

loss, a higher complication rate, and a higher cost.[9] In a study that compared thermal ablation with surgical resection, no differences in OS and disease-free survival were reported between the groups.[10] The rate of major complications, however, was significantly higher in the resection group than in the thermal ablation group (P <.001).[10] In patients with large, recurrent tumors (ie, >3 cm in diameter), OS was significantly higher in those undergoing resection (P = .037).[10]

Based on studies of ablation, the following conclusions can be drawn:

- Ablation can be considered if the lesion is <3 cm
- A wide ablation zone (>1 cm) should be used
- Combination therapy with embolization may be considered with larger tumor size
- Ablation is preferred for patients who are not surgical candidates because of comorbidities or lesion location, since surgery is still the standard of care
- Ablation is likely a better approach for patients who have recurrent intrahepatic CCA after a surgical resection.

Radioembolization

The use of radioembolization was assessed in a systematic review of 9 relatively small observational studies that included a total of 224 patients.[11] Patients with the mass-forming type of intrahepatic CCA had a significantly better median OS than those with the infiltrative type (19.9 months vs 8.1 months, respectively).[11] Moreover, patients with treatment-naïve CCA had a longer OS than those who had received therapy prior to radioembolization. Patients who were receiving concurrent chemotherapy had significantly better OS compared with those who were not receiving chemotherapy (19.5 months vs 5.5 months, respectively; P = .042).[11]

The largest published series of patients undergoing radioembolization for intrahepatic CCA is from a retrospective study of all individuals (N = 85) who were not surgical candidates and were ineligible for chemotherapy.[12] The median OS from diagnosis was 21.4 months (95% confidence interval [CI], 16.6-28.4), and the median OS from treatment with radioembolization was 12.0 months (95% CI, 8.0-15.2).[12] No 30-day mortality was reported following radioembolization therapy. Survival was assessed based on imaging characteristics; no difference could be detected in median OS between hypo-enhancing or hyper-enhancing tumors or between mass-forming or infiltrative tumors.[12]

Large-scale prospective clinical trials are warranted, to better define the role of liver-directed therapies.

Hepatic artery infusion pump

Intrahepatic CCA is a primary liver tumor that is often locally advanced but not metastatic at the time of presentation. Importantly, these tumors derive their blood supply predominantly from the hepatic arterial system, providing the rationale behind use of a hepatic arterial infusion pump. Floxuridine (FUDR) for use in the infusion pump is a 5-fluorouracil (5-FU) analog with extensive first-pass liver uptake and high efficacy against intrahepatic CCA. FUDR has high hepatic exposure, which is 100-fold to 400-fold higher than that of other agents used for hepatic arterial infusion.[13]

A phase 2 study of hepatic arterial infusion of FUDR in combination with systemic gemcitabine and oxaliplatin in 38 patients with unresectable, nonmetastatic intrahepatic CCA demonstrated a 58% partial radiographic response rate and an 84% disease control rate at 6 months.[14] Overall, 4 patients experienced a sufficient response to undergo surgical resection. With a median follow-up of 30.5 months, the median progression-free survival (PFS) was 11.8 months and the median OS was 25.0 months.[14] Toxicities were manageable and tolerable, with elevated levels of liver enzymes being the most common grade ≥3 adverse event.[14]

Role of radiation

In patients with intrahepatic CCA, palliative doses of radiation have been replaced by ablative radiotherapy doses over time, as imaging guidance, proton beam radiation, and intensity-modulated radiation therapy became available. This has resulted in clear improvements in patient outcomes, with local tumor control rates as high as 80% and 4-year OS as high as 75%.[15] Of the patients who received lower doses of radiation, 89% died of tumor-related liver failure.[15]

In a phase 2 study, 37 patients were treated with 3 to 5 weeks of ablative radiation over 3+ years, typically in a later-line setting following hepatic arterial infusion pump therapy or chemotherapy with progression.[16] Overall, 60% of the patients had extrahepatic disease. Local tumor PFS was 80% and median OS was 33.5 months.[16]

An ablative dose of radiation can be administered over 1 week, 2 weeks, 3 weeks, or 5 weeks. The choice is dependent on the size of the tumor and how much of the liver and/or gastrointestinal tract needs to be protected.

With both gallbladder cancer and intrahepatic CCA, there is a high risk for developing distant metastases. Moreover, in such patients, the likelihood of an isolated local recurrence following surgery is low, which limits the role of adjuvant chemoradiation for this indication.

Radiation in the adjuvant setting

Radiation therapy is controversial in the adjuvant setting for biliary tract cancer. In patients with CCA, the data regarding radiation are of poor quality, consist-

ing mainly of single-institution retrospective reviews; large databases with limited single patient details; and a mix of patients with hilar, distal bile duct, and gallbladder cancers.

Extrahepatic cholangiocarcinoma

Most studies of adjuvant radiation for patients with extrahepatic CCA demonstrated an improvement in local-regional control, with a suggestion of an improvement in OS in some series. The caveat with respect to single-institution studies is the potential for patient selection bias: Patients with better performance status may be selected for chemoradiation.

A meta-analysis of 20 studies including 6712 patients found that adjuvant radiation therapy appears to have a significant benefit only in those with positive resection margin (R1), regardless of disease site, in the end point of OS.[17] In contrast, radiation therapy was associated with nonsignificant odds of harm among patients with R0 resection.[17]

Prospective data from the single-arm, phase 2 Southwest Oncology Group (SWOG) S0809 study of high-risk patients with extrahepatic CCA or gallbladder cancer were evaluated. Patients were treated with gemcitabine and capecitabine for 4 months, followed by chemoradiation.[18] Rates of 2-year OS were promising, exceeding 60%. On subgroup analysis, the addition of radiation nearly negated the adverse impact of R1. The overall local failure rate was 21% in the distal bile duct. For hilar CCA, the local failure rate was 23%.[18]

The National Comprehensive Cancer Network (NCCN) guideline for the management of extrahepatic CCA lists chemoradiation as a postresection treatment option in patients with R0 or R1 resection, with similar recommendations for gallbladder cancer.[19] Chemoradiation is not recommended in the R0 setting in patients with intrahepatic CCA.[19]

Liver Transplantation

Hilar cholangiocarcinoma

Based on the observation that a select few patients with early-stage disease achieved long-term survival, combined with the finding that radiation provided palliation and, in rare cases, prolonged survival, the Mayo Clinic team in Rochester, MN, initiated a radiation protocol for patients with unresectable hilar CCA.[20,21] This protocol combines neoadjuvant radiation and chemotherapy, in the form of external beam radiotherapy with bolus 5-FU, followed by brachytherapy and oral capecitabine, a formal exploratory laparotomy to rule out metastases or local extension of the tumor (which would preclude complete resection), then orthotopic liver transplant (OLT) either from a living donor or from a deceased donor.[21] Staging is important to detect peritoneal disease and rule out node-positive disease.

Eligibility criteria include a malignant-appearing stricture and ≥1 of the following: (1) malignant cytology or histology, (2) an elevated CA 19-9 without cholangitis, or (3) polysomy detected by fluorescence in situ hybridization (FISH). The cancer should be located primarily above the cystic duct. The cancer must be unresectable (de novo CCA) or cancer arising in the setting of primary sclerosing cholangitis (PSC). Excluded patients were those with a mass >3 cm into the parenchyma, those who have undergone prior attempted resection with violation of the tumor plane, and those in whom transperitoneal biopsy was performed.[22] Combined neoadjuvant therapy plus liver transplantation achieved favorable results for unresectable patients with perihilar CCA.

Results from a study of 211 patients who proceeded to liver transplantation show 69% survival at 5 years posttransplant and 62% at 10 years.[23] Patients with PSC had superior outcomes, possibly because they had been on surveillance and were captured earlier. A histologic response to the neoadjuvant therapy is one of the keys to a successful outcome, the reason for which is not well understood. When adjusted for age, stage, and presence of PSC, residual tumor was still the key predictor of recurrence.[23]

Liver transplantation may also be appropriate for patients with potentially resectable de novo hilar CCA. The experience at 10 US centers of patients with perihilar CCA undergoing resection versus transplant reveals superior 3-year survival (72% vs 33%, respectively) and 5-year survival (64% vs 18%, respectively) with transplantation.[24] Resection for the patients who met the transplant criteria was associated with worse survival. Prospective trials are warranted and justified.[24]

Intrahepatic cholangiocarcinoma

OLT can be performed in patients with unresectable intrahepatic CCA, with excellent outcomes, and may exhibit survival advantages compared with resection.

In a single-center, comparative analysis of resection versus OLT for intrahepatic or hilar CCA of >24-year duration, patients who underwent OLT fared much better than did those who underwent surgical resection.[25] Among those undergoing OLT, neoadjuvant plus adjuvant therapy significantly improved outcomes compared with adjuvant therapy alone or no adjuvant therapy (P = .03), with OS approaching 60% in the neoadjuvant/adjuvant therapy group.[25] Factors that predicted worse survival outcomes on multivariate analysis were hilar CCA, multifocal tumors, perineural invasion, and resection compared with OLT as the treatment modality. Tumor size was not a predictor of poor outcome.[25]

Liver transplantation for "very early" intrahepatic CCA (ie, a single tumor ≤2 cm) was shown to be associated with a low risk for recurrence.[26] Among a group of patients who were transplanted for hepatocellular carcinoma or decompensated cirrhosis who were found to have intrahepatic CCA at explant pathology, the 1-, 3-, and 5-year cumulative risks for recurrence were 7%, 18%, and 18%, respectively, after a median follow-up of 35 months in those with very early intrahepatic CCA. Moreover, the 1-, 3-, and 5-year survival rates in this same patient population were 93%, 84%, and 65%, respectively.[26]

According to the Methodist–MD Anderson (Houston, TX) protocol, 6 months' duration of stability under neoadjuvant therapy might be an appropriate surrogate marker for the selection of patients with biologically favorable disease for OLT.[27] Imaging is repeated every 3 months and has to demonstrate stable or regressing disease. Among 21 patients with intrahepatic CCA referred for OLT, 6 received transplantation.[27] Most tumors were stage T2; the median maximum lesion size was 7.4 cm, and the median total diameter of the lesions was 10.4 cm. Explant characteristics were as follows: the number of lesions was 3, the median maximum lesion size was 6.0 cm, and the median total diameter of the lesions was 8.5 cm. The 5-year survival rate following OLT was 83.3%.[27]

Before Surgery: Sequencing Neoadjuvant Therapy

Neoadjuvant treatment has both advantages and disadvantages. Although more patients will receive treatment, the risk for overtreatment is real, as observed in those with limited-stage disease. Neoadjuvant therapy may obviate surgery in those who progress rapidly because of poor biology, but the downside is that it will delay potentially beneficial surgery and some patients may not be able to proceed to surgery at all.

Disease biology appears critical for patient selection for neoadjuvant therapy. In the BILCAP study, treatment with neoadjuvant capecitabine had no effect on survival with R1 resection but improved survival with R0 resection.[28] Whether R1 resection reflects disease biology or simply the size of the cancer itself is uncertain. An apparent lack of benefit to neoadjuvant treatment was observed in patients with perihilar CCA, whereas those with extrahepatic CCA appeared to benefit despite a similar R1 resection rate.

The goal of neoadjuvant therapy is to eradicate micrometastases and to improve the rate of margin-negative resection in patients with technically resectable disease. Data on neoadjuvant treatment in patients with CCA are sparse. The greatest obstacle to conducting clinical trials on neoadjuvant therapy in CCA is its rarity, so multi-institutional, multinational collaboration is warranted. Furthermore, since most intrahepatic and hilar CCAs are not resectable at presentation, patients cannot be enrolled in a neoadjuvant trial. Finally, a preoperative tissue diagnosis is usually required to enroll in a trial, which can be difficult to obtain in patients with hilar CCA.

The largest experience with neoadjuvant therapy in CCA comes from the selection of patients for transplantation who have already met transplant inclusion criteria. The goal of neoadjuvant therapy in this setting is to eradicate micrometastatic disease and help to select those patients who will achieve a better outcome with transplant. The challenges associated with neoadjuvant therapy in the resectable setting are numerous, including preoperative tissue diagnosis and the need for SpyGlass endoscopy or FISH analysis as a complement to biopsy to make the diagnosis.

In the intrahepatic resectable CCA setting, 5-year OS is 31%, so the room for improvement with neoadjuvant therapy is considerable.[29] Clinical trials of neoadjuvant therapy in intrahepatic CCA were initially conducted in the metastatic setting, but it took 4 years to accrue the data and an additional 3 to 5 years for follow-up. Therefore, the lag of extrapolation of data to patients with resectable disease was about a decade.

An ongoing study is testing the hypothesis that neoadjuvant therapy with gemcitabine, cisplatin, and nab-paclitaxel is feasible, will increase resectability rates, and will improve recurrence-free survival and

OS for patients with resectable oncologically high-risk intrahepatic CCA.[30]

After Surgery: Sequencing Adjuvant Therapy

A clear consensus on the standard of care for patients following resection for biliary tract cancer has been difficult to achieve. For many years, a lack of collaboration and the use of small retrospective studies have limited the ability to definitively determine a benefit for treatment. Recent larger trials have been conducted with more statistical rigor and are having an impact on the care of patients with biliary tract cancers.

Pooled data from a 2012 systematic review/meta-analysis of 20 studies (mentioned earlier in this section) that included 6712 patients showed a trend to improved survival with adjuvant therapy in the treatment of biliary tract cancer, specifically for R1 resection, with a suggestion that chemotherapy or chemoradiation was better than radiation alone.[17]

The best prospective data for the use of adjuvant therapy in patients with biliary tract cancer come from the randomized, controlled, multicenter, phase 3 BILCAP study.[31] Although capecitabine did not improve OS over observation in the intention-to-treat population, "the prespecified sensitivity and per-protocol analyses suggest that capecitabine can improve overall survival in patients with resected biliary tract cancer when used as adjuvant chemotherapy following surgery and could be considered as standard of care."[31]

No controlled trials have demonstrated a benefit with adjuvant chemoradiation over surgery alone in patients with biliary tract cancer, although many retrospective studies suggest superior outcomes with adjuvant therapy. Adjuvant therapy may have a role in those patients with an incompletely resected tumor.

Extrahepatic cholangiocarcinoma

In a randomized study of patients with resected periampullary adenocarcinoma, participants were assigned to observation, adjuvant gemcitabine, or 5-FU/leucovorin.[32] After adjustment for independent prognostic variables, chemotherapy was superior to observation with respect to OS. Because of the small number of patients with biliary cancer, the effect of treatment on survival in this group was not reported.[32]

Intrahepatic cholangiocarcinoma

In patients with intrahepatic CCA, adjuvant chemotherapy and chemoradiation improved outcomes in patients with positive margins or positive lymph nodes, but the benefit was absent in those with negative margins or negative lymph nodes. In the Taiwan Cancer Registry analysis, superior OS was achieved with chemoradiation compared with chemotherapy alone in patients with positive margins or stage III or IV intrahepatic CCA.[33]

"What I took away from this study the most is that the sequential chemotherapy followed by radiation therapy wasn't as beneficial as the combination of chemotherapy with radiation," one of the audience members noted.

Gallbladder cancer

In a phase 3, multicenter, prospective, randomized, controlled trial, surgery plus mitomycin C and infusional 5-FU improved 5-year OS in patients with resected gallbladder cancer, but the benefit appeared to be limited to patients deemed to have a "noncurative" resection.[34] There was no benefit to adjuvant therapy in bile duct or ampullary cancers, regardless of the type of resection.

In patients with gallbladder cancer, the benefit of adjuvant chemoradiation appears to be modest, based on an analysis of the National Cancer Database.[35] The best prospective data in this setting are from SWOG S0809, in which adjuvant capecitabine and gemcitabine followed by radiotherapy led to a high 2-year OS rate, with similar OS and local control in patients with R0 and R1 resections.[18] A major limitation of SWOG S0809 was the lack of a concurrent control arm.[18]

CHORUS DISCUSSION

Chorus members were asked whether they offered local therapy to patients with intrahepatic CCA who were not candidates for surgery. More than half (55%) indicated that they did. When asked about their preferred local therapeutic modality for patients with inoperable intrahepatic CCA, the audience was split evenly between ablative external beam radiation therapy administered at 100 Gy in 15 to 25 fractions and radioembolization with Y-90 (33% each), whereas 22% would opt for hepatic artery chemoperfusion and 11% would select conventional dose radiation therapy (50.4 Gy in 28 fractions). The chorus members emphasized the importance of an adequate dose of radiation to achieve maximum benefits if radiation is to be used in this setting.

The sequencing of systemic chemotherapy relative to liver-directed therapy for patients with localized, yet inoperable CCA was discussed, with one chorus member noting that 70% of patients receive chemotherapy prior to radioembolization, which improves survival compared with no chemotherapy. Another member commented that the sequencing of chemotherapy depends on the local treatment. For example, with hepatic arterial infusion, chemotherapy would be administered concurrently. The sequencing of local-regional therapy may also be important, as it could affect subsequent choices of local-regional therapy.

According to one chorus member, for nonsurgical

candidates, one must differentiate between a nonsurgical candidate for resection and a nonsurgical candidate for transplant. "Obviously, transplant is making its way into those patients," he stated. "We're still going to resect patients if they have localized disease. Having said that, those modalities are going to be employed when you are unable to do a primary resection. We use these as temporizing measures, so which temporizing measure is better? With a multifocal T2 lesion, I probably would start thinking about a transplant."

With intrahepatic CCA, targets for transplant depend on the ability to contain the tumor locally, noted another presenter. "Of patients who have liver disease only, without metastatic disease, chemotherapy is successful in containing the tumor about 50% of the time," he indicated. "That gives us 50% of the patients with T2 nonmetastatic disease as potential targets for transplant."

Selection is key to transplantation in hilar CCA as well, said another audience member "in that you need to exclude people with metastatic disease." ■

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