Updates in Cholangiocarcinoma

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Abstract

Cholangiocarcinoma is a spectrum of invasive adenocarcinomas that arise in the intrahepatic, perihilar, or distal biliary tree, and is classified by location. During JADPRO Live Virtual 2021, Kristen O'Hagan, MSN, RN, ANP-BC, AOCNP®, discussed this complex disease, current treatment strategies, and the role of targeted therapy and how it's changing the treatment landscape for cholangiocarcinoma.

A rare and deadly cancer, the incidence of cholangiocarcinoma is on the rise, and prognosis remains dismal. For patients with resectable disease, the 5-year survival rate is between 15% to 25%, and for those with metastatic disease, the survival drops to only 2% at 5 years. The recent approvals of two targeted agents, however, could represent a turning point for this disease.

During JADPRO Live Virtual 2021, Kristen O'Hagan, MSN, RN, ANP-BC, AOCNP®, a nurse practitioner at Memorial Sloan Kettering Cancer Center, described the different types of cholangiocarcinoma as defined by location and identified current treatment strategies for patients with this disease. Ms. O'Hagan also discussed the role of targeted therapy in the cholangiocarcinoma treatment landscape.

BACKGROUND

A spectrum of invasive adenocarcinomas that arise in the intrahepatic, perihilar, or distal biliary tree, cholangiocarcinoma is diagnosed in approximately 8,000 people annually in the US, but its incidence is on the rise. The disease is also more prevalent in Asia. The annual mortality rate for cholangiocarcinoma is 2 deaths per 100,000 inhabitants in the US, but that number is 3 times higher in Asia (Banales et al., 2020).

According to Ms. O'Hagan, the pathogenesis of cholangiocarcinoma remains a mystery in approximately 50% of patients diagnosed with the disease, but for the other half, there are identifiable risk factors. These risk factors are associated with inflammatory conditions such as primary sclerosing cholangitis, Caroli disease, hepatolithiasis, cirrhosis (hepatitis infection or nonalcoholic steatohepatitis), and liver fluke infections.

Ms. O'Hagan also noted variations in mortality across race and gender. Male gender is associated with increased mortality risk overall. Asian ethnicity accounted for highest mortality risk in both genders, but Hispanic woman also have an increased mortality.

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In addition, African Americans' risk of dying from cholangiocarcinoma is increasing more rapidly compared with other ethnic groups (Yao et al., 2016).

Cholangiocarcinoma is also associated with socioeconomic and racial disparities, said Ms. O'Hagan, who noted that receipt of surgery is influenced by socioeconomic status and race, with African Americans, Hispanics, Asians, and Medicaid patients being less likely to have surgery (Ransome et al., 2019).

TUMOR LOCATION DEFINES THE DISEASE

Cholangiocarcinoma is a heterogeneous disease defined by tumor location. Tumor location influences the type of symptoms at presentation, the surgery to be performed, and the prevalence of genetic mutations.

Patients with intrahepatic cholangiocarcinoma, for example, can present with abdominal pain.

"The liver has few pain fibers, and they're only on the surface, but if the tumor is on the surface and stretching it, you're going to have pain," said Ms. O'Hagan. "However, these patients can also be asymptomatic."

In patients with established chronic liver disease, cholangiocarcinoma symptoms may include splenomegaly, ascites, spider naevi, gynecomastia, caput medusae, and encephalopathy. Those with perihilar and distal cholangiocarcinoma, on the other hand, present with biliary obstruction and can have jaundice, pale stools, and itching (Valle et al., 2021).

Tumor location will also influence surgery. Intrahepatic cholangiocarcinoma is treated with a partial hepatectomy and may also require a bile duct excision and reconstruction. Perihilar cholangiocarcinoma requires a bile duct excision and reconstruction. Finally, distal cholangiocarcinoma is treated with pancreaticoduodenectomy or Whipple procedure.

"Surgery is the only driver for a cure right now in this disease, and surgery needs to be done in high-volume specialty centers to have the best outcomes for patients," said Ms. O'Hagan.

"It takes a village to take care of these patients," she explained. "They need a group of advanced practitioners that understand cholangitis, biliary drainage, and all the things that go along with this disease."

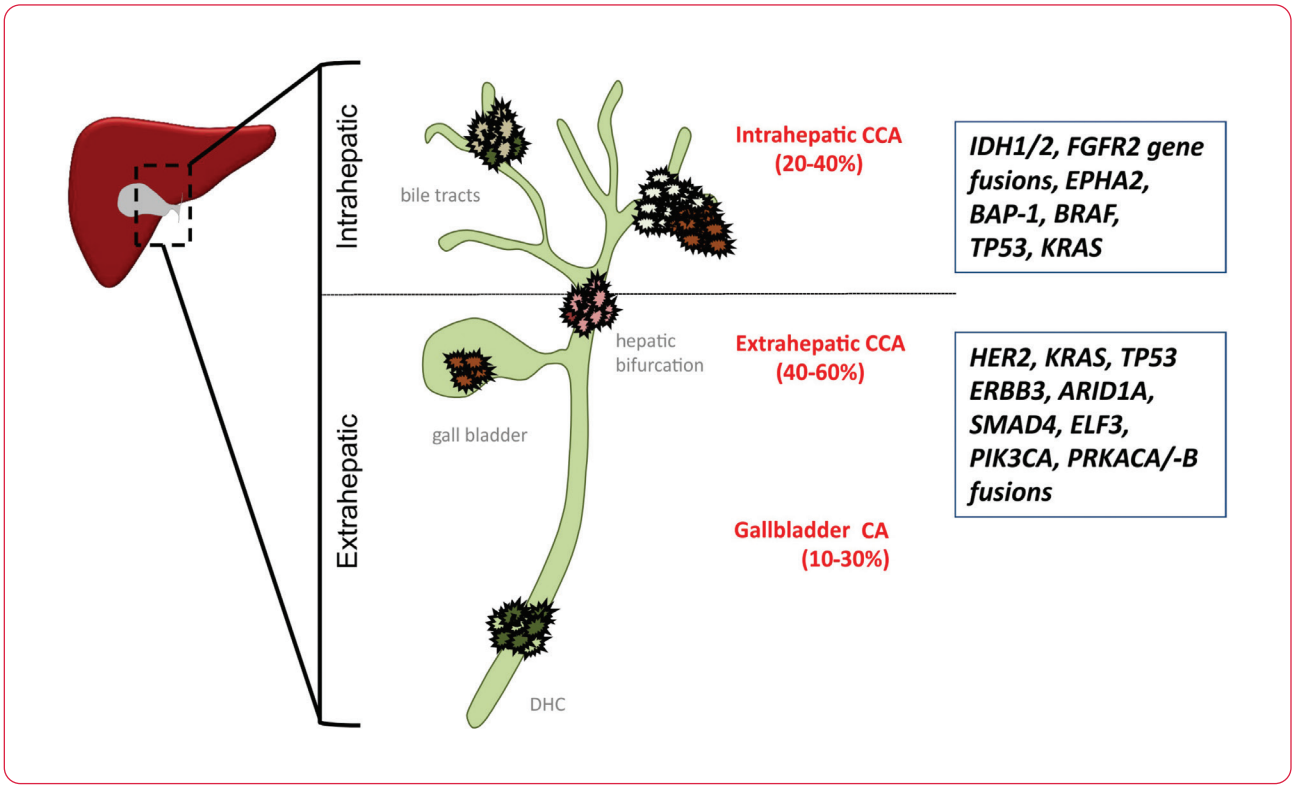

Figure 1. Location = mutations.

Finally, tumor location influences mutations. Intrahepatic cholangiocarcinoma is associated with *IDH1/2*, *FGFR2* gene fusions, *EPHA2*, *BAP-1*, *BRAF*, *TP53*, and *KRAS* mutations (Czauderna et al., 2021; Figure 1).

Extrahepatic disease is associated with *HER2*, *KRAS*, *TP53*, *ERBB3*, *ARID1A*, *SMAD4*, *ELF3*, and *PIK3CA* mutations.

Cholangiocarcinoma presents some unique challenges with regards to detecting genetic alterations. Aside from the intrahepatic cholangiocarcinoma, a core biopsy is difficult for many cholangiocarcinomas because they are small tumors in hard-to-reach locations. Genetic mutations may not be measured until second- or third-line therapy, often when there is a metastatic site to target with biopsy.

"Cholangiocarcinoma harbors many genetic mutations, which is good news, but not all patients have genetic mutations, and not all mutations have a targeted therapy," said Ms. O'Hagan. "However, these mutations should play an increasingly important role in the future treatment with advancements in targeted therapies."

TENETS OF TREATMENT

Surgery offers the only curative treatment for cholangiocarcinoma, but only 22% of patients are operable at presentation. Consequently, for approximately 80% of patients with metastatic disease or recurrence after surgery, palliative chemotherapy represents the only treatment course. Best supportive care, which includes anticipating infections and biliary obstructions, is associated with a survival benefit, too.

First-line therapy for cholangiocarcinoma is cisplatin plus gemcitabine based on 2010 data that showed superior overall survival with the combination vs. gemcitabine monotherapy (11.7 months vs. 8.1 months; Valle et al., 2010).

"11 years later, this is still first-line therapy for cholangiocarcinoma, so we need to make some improvements here," said Ms. O'Hagan.

Adjuvant therapy is a recent addition to the treatment armamentarium. The phase III BILCAP trial demonstrated a survival benefit following treatment with capecitabine for 6 months post-resection, and this was approved by the U.S. Food and Drug Administration (FDA) in 2019 (Primrose et al., 2019).

SECOND-LINE CHEMOTHERAPY

FOLFOX became the standard second-line chemotherapy based on data from the ABC-06 study that showed a 1-month improvement in overall survival and a 15% increase in 6-month and 12-month overall survival rates (Lamarca et al., 2021).

"These weren't impressive data, but there was a little bit of a survival benefit," said Ms. O'Hagan.

An abstract presented at the 2021 ASCO Annual Meeting, however, showed better outcomes for patients with biliary tract cancer who received liposomal irinotecan in combination with fluorouracil (5-FU) and leucovorin (Yoo et al., 2021). The multicenter study demonstrated a nearly 6-month improvement in progression-free survival and a 3-month improvement in overall survival with the addition of liposomal irinotecan to 5-FU and leucovorin in patients who had progressed on gemcitabine plus cisplatin.

"This may be the new second-line therapy for cholangiocarcinoma, which would be good news for patients," said Ms. O'Hagan.

PEMIGATINIB

Pemigatinib (Pemazyre), the first approved targeted therapy for cholangiocarcinoma, was approved in the second or third line for patients with *FGFR2* fusions or rearrangements. The pivotal study demonstrated a progression-free survival of 6.9 months and an objective response rate of 35% (Abou-Alfa et al., 2020a).

"This treatment is a major breakthrough," said Ms. O'Hagan, who noted that approximately 15% of patients harbor this mutation.

Hyperphosphatemia is a major side effect experienced by 60% of patients.

Pemigratinib is currently being studied in the first line as monotherapy and in combination with gemcitabine plus cisplatin.

IVOSIDENIB

Another targeted agent approved in the second or third line is ivosidenib (Tibsovo), a selective and reversible mutant IDH1 inhibitor for *IDH1*-mutant cholangiocarcinoma. Progressive-free survival increased from 2.7 months with placebo to 6.9 months with ivosidenib, and the median overall survival improved an additional 3 months in the pivotal study (Abou-Alfa et al., 2020b).

The treatment is also generally well tolerated. The only major grade 3 side effect was ascites, which is thought to be more related to disease progression than the medication, said Ms. O'Hagan.

"It's a select population, but we're seeing great responses," said Ms. O'Hagan, who noted that *IDH1* mutations are seen in approximately 13% of intrahepatic cholangiocarcinoma. "With new targeted therapies approved, and more actively being studied, this may be cholangiocarcinoma's watershed moment."

ACTIONABLE MUTATIONS

For the small subset of patients with biliary cancers who harbor *NTRK* mutations (less than 5%), Larotrectinib (Vitrakvi) is another option. A phase I/II study involving adults and adolescents demonstrated marked and durable antitumor activity in patients with *TRK* fusion-positive cancer, regardless of the age of the patient or of the tumor type (Drilon et al., 2018). Response rates approached 75%, and 1-year progression-free survival was 55% among patients receiving larotrectinib.

Finally, for patients with microsatellite instability or mismatch repair deficiency, the PD-1 inhibitor pembrolizumab (Keytruda) recently demonstrated 40.9% response rate and an overall survival of more than 2 years (Marabelle et al., 2020).

"This was a basket trial, and there were only a couple of patients with cholangiocarcinoma enrolled, but those are pretty impressive outcomes for this disease," said Ms. O'Hagan.

Disclosure

The presenter had no conflicts of interest to disclose.

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