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Rethinking Approaches to Biliary Tract Carcinoma

Announcer:

Welcome to CME on ReachMD. This activity, titled “Rethinking Approaches to Biliary Tract Carcinoma,” is provided in partnership with TOPEC Global and supported by an independent educational grant from Merck KGaA, Darmstadt, Germany.

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Dr. Borad:

Although uncommon, which biliary tract carcinoma presents formidable diagnostic and treatment challenges, which is why it's so important to stay up-to-date on the pathophysiology of the disease, the current first- and second-line treatments, and the latest clinical trials. Fortunately, that's exactly what we're going to focus on today. I'm

Dr. Mitesh Borad from Mayo Clinic, and I'm today speaking with my colleague, Dr. Milind Javle, from MD Anderson.

Dr. Javle, it's great to get a chance to speak with you again today.

Dr. Javle:
Thank you, Dr. Borad.

Dr. Borad:
Setting the stage for our viewers today, Dr. Javle, can you quickly highlight what would be included under biliary tract cancers? Is it 1 disease or several diseases together?

Dr. Javle:

So, biliary tract cancer is actually 3 different diseases—gallbladder cancer, intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma. These are grouped as one, but they have differing etiologies and, indeed, differing prognosis and sometimes therapies

So, biliary tract cancer is a disease of chronic inflammation—for instance, in gallbladder cancer often related to gallstones, in cholangiocarcinoma related to infections. There are important regional and incidence differences. For instance, in Japan, in China, in East Asia, it's often associated with hepatitis B infection, in certain areas of the Far East with liver fluke infection. In Europe and the United States, on the other hand, there is a link between biliary tract cancer or cholangiocarcinoma and primary sclerosing cholangitis, as well as intrahepatic cholangiocarcinoma a link with obesity and NASH, or fatty liver.

Dr. Borad:

Now, I recently saw an estimate that more than 65% of patients with a diagnosis of BTC present with nonresectable disease and that their prognosis is typically poor. So, in your opinion, Dr. Javle, what are the signs and symptoms of BTCs, and why are they so difficult to diagnose at an earlier stage?

Dr. Javle:

So, biliary tract cancers, as you appropriately highlighted, are often diagnosed at an advanced, unresectable stage. Let me give you an example of intrahepatic cholangiocarcinoma. These tumors can grow to a considerable size before they cause biliary tract obstruction, and often I discovered, due to ill-defined abdominal discomfort or alteration in liver function tests, due to the uncommon nature of this disease, often patients are seen by their family practitioners, and this is not the most common or the most frequent diagnosis because these symptoms can mimic several non-cancer diagnoses as well. So, as a consequence, these diseases are often discovered quite late when surgery becomes impossible. I believe that is an important factor why the prognosis of biliary tract cancer is so low.

Dr. Borad:

Continuing on to the treatments for biliary tract cancers, can you highlight what are the current

standard first- and second-line treatments in this disease?

Dr. Javle:

So, the first-line treatment for advanced unresectable biliary tract cancer is based on the ABC-02 trial from the United Kingdom, now almost 10 years ago, and that is gemcitabine and cisplatin. The second-line treatment approach is not yet defined. ABC-06 trial, which tested the regimen of FOLFOX versus placebo, will be discussed at the ASCO 2019 meeting. Hopefully, that creates a new standard in treatment. In terms of surgical resection, as you mentioned earlier, very few patients, less than 20%, are appropriate for surgical resection. Clearly, if patients have localized disease, surgery is the only potential option that can provide cure, so if the patient is diagnosed at an earlier stage in either biliary tract cancer, then surgery sometimes followed by additional treatment is the standard of care today.

Dr. Javle:

For those joining us, this is CME on ReachMD. I'm Dr. Milind Javle, and today I'm speaking with Dr. Mitesh Borad from Mayo Clinic about biliary tract cancer, or BTCs.

Dr. Javle:

So, first of all, I'd like to get your opinion of identifying the greatest unmet needs for patients diagnosed with BTC. Where are we struggling the most for these patients? Can you discuss the perspective of the most pressing unmet needs in diagnosis and treatment for BTCs?

Dr. Borad:

Yeah, I'll quickly highlight. With diagnosis, it is difficult to diagnose these patients early enough, so little things, say, like liquid biopsy become important in that aspect. With regards to treatment, you highlighted that the current standard approaches are cytotoxic chemotherapies. While they seem to help patients live longer, the number of patients having durable responses is quite low, and this is where I think approaches such as immunotherapy will really have a big role. Like other tumors, the immune checkpoint inhibitors have been evaluated. This includes things such as nivolumab and pembrolizumab. Unfortunately, the response rates have sort of been in the less than 10% range in larger studies, albeit in the patients where these do occur, relatively durable.

There are some newer agents that appear to be very exciting. One that I would want to highlight is M7824, also known as Bintrafusp alpha. This is a very unique molecule with bifunctional capabilities where 1 domain binds to PD-L1 and the second domain is TGF beta receptor 2 extracellular domain that binds to TGF beta, which is thought to be an immunosuppressive moiety in the tumor microenvironment. In early studies it has shown response rate of about 20%. However, the key thing here is that these responses are quite durable, lasting anywhere from 8 to 14 months thus far. Immunotherapy, I feel, is really the area where a lot of investigation will occur in this disease, and we

hope to see results from larger, later-stage trials with this types of drugs.

Dr. Borad:

So, Dr. Javle, as we come to a close here, is there anything you would like to highlight for our viewers today?

Dr. Javle:

Thank you, Dr. Borad. BTC is really an exciting area of research, particularly now, whereas there were very, very few trials even as recently at 10 years ago. Areas that I would want to highlight are cytotoxic chemotherapy. There are 2 important trials that I would highlight in Europe for FOLFIRINOX, which is gemcitabine and cisplatin. It's a phase II randomized study. Here in the US, based on some work that was done with you at Mayo Clinic, and MD Anderson, gemcitabine cisplatin abraxane, a 3-drug regimen, is being investigated in a phase III trial against gemcitabine and cisplatin.

A particularly exciting area is within the realms of targeted therapy. So, as you know, there are multiple actionable mutations in these cancers. I just highlight 2 with IDH1 mutations where a phase III trial has been completed with AG-120. There are at least 4 ongoing trials with FGFR inhibitors, and we will get the readout very soon. And as you mentioned earlier, there are immunotherapy trials in this space, such as the exciting trial with M7824.

Dr. Javle:

And my last question for you, Dr. Borad: Are there any takeaways from what you and I talked about earlier or maybe something we haven't yet covered that you want to share for the audience?

Dr. Borad:

I think we should just summarize that while these are uncommon cancers, there seems to be a lot going on in terms of clinical trials, whether it be immunotherapy, precision medicine, or even standard cytotoxics, and it has become a robust environment for investigation; and hopefully, these will lead to advances that will help patients.

Dr. Javle:

Well, unfortunately, it's that time to draw this program to close, but it's been great discussing biliary tract cancers together. Thank you for joining me, Dr. Borad.

Dr. Borad:

It's been great fun discussing biliary tract cancers with you, Dr. Javle, today. We thank our viewers for their attention and hope to speak soon again.

Announcer:

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