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### Biliary Tract Carcinoma: Are We at the Point of Change?

Dr. Hamid:

This is CME on ReachMD, and I'm Dr. Hamid. Joining me to discuss new approaches that may in time improve outcomes for patients with biliary tract carcinoma, or BTC, is Dr. Oh from Seoul National University College of Medicine in Seoul, Korea.

So, to get us started, Dr. Oh, what are the major molecular approaches being considered for the treatment of BTC?

Dr. Oh:

Yes, very important question. So, as you know, in biliary tract cancer, so far we haven't had such a good weapon to fight against this tumor. For example, in advanced biliary tract cancer, the first-line standard-of-care treatment is gemcitabine and cisplatin combination, or therapy, based on the ABC-02 trial. And in second-line setting of advanced biliary tract cancer, we haven't had good randomized trials so far even though we have treated the patients with 5-FU-based chemotherapy so far.

Very recently, ABC-06 trial reported very interesting data which compared the cytotoxic chemotherapy—in ABC-06 this case they used the modified FOLFOX—and they compared it with the active symptom control in second-line biliary tract cancer patients, and in this case the chemotherapy improved the patient survival compared to the active symptom control. So, now we have first-line gemcitabine cisplatin chemotherapy and second-line 5-FU-based chemotherapy. That's all we have with good evidence so far to treat the patients with advanced biliary tract cancer.

Biliary tract cancer has really interesting, many, many good molecular alterations which can be targeted from the drug development point of view. For example, IDH1 mutation is one of the candidate genetic alterations found in, especially, intrahepatic cholangiocarcinoma. And nowadays, there are clinical trials using mutant IDH1 inhibitors in this population.

Another interesting genetic alteration in biliary tract cancer is FGFR alterations. Among them, especially FGFR2 fusion, is quite an interesting therapeutic target. So, FGFR inhibitors have shown already good response rate in progression-free survival in chemotherapeutic refractory biliary tract cancer patients with FGFR2 fusion. So, nowadays, there are several FGFR inhibitors competing in this field out there.

Another interesting target would be the HER2, like HER2-positive gastric cancer or HER2-positive breast cancer. Yes, biliary tract cancer also has HER2 alteration; especially the gallbladder cancer has a high incidence of HER2 alteration. So, nowadays, targeting HER2 in biliary tract cancer is an study.

Dr. Hamid:

And just to follow up on the approaches you just mentioned, the evidence that immunotherapy, and more specifically, immune checkpoint inhibitors, may have a role in the management of BTC continues to grow. So, with that being said, what can you share with us about the data?

Dr. Oh:

Yes, the drug development point of view... So, nowadays, immunotherapy has really prevailed in all kinds of solid tumors; so why not in biliary tract cancer? So far we have several evidences of using immune checkpoint inhibitors in biliary cancer. For example,

pembrolizumab monotherapy has been tested in chemorefractory biliary tract cancer patients. Keynote-028 targeted the patients with PD-L1 expression in chemorefractory biliary cancer. Another one is Keynote-158 study. In this case, biliary tract cancer patients with chemorefractoriness were enrolled largely PD-L1 status.

In Keynote 028, which enrolled only PD-L1-positive chemorefractory biliary tract cancer patients, the response rate of pembrolizumab monotherapy was 13%. And in the case of Keynote 158, the patients with chemorefractoriness but regardless of the PD-L1, when they are treated with pembrolizumab monotherapy, the overall response rate is 5%. And the overall survival in both trials ranged 5 to 7 months, so the pembrolizumab monotherapy in chemorefractory biliary tract cancer is, I think, modest. Very similar evidence is from the Japanese colleagues. They used nivolumab in this study in, again, similar chemorefractory biliary tract cancer patients. They enrolled regardless of the PD-L1 status of the patient. And again, the nivolumab monotherapy produced 3.3% overall response rate and 5-month overall survival.

Again, so far we can say that immune checkpoint inhibitor monotherapy in chemorefractory biliary tract cancer, the efficacy is modest. So, to improve the treatment outcome, definitely we need another—different strategies like combination strategies so we can target immunocompetent or we can think about a combination of immune checkpoint inhibitors with cytotoxic chemotherapy, something like that.

Dr. Hamid:

Okay, so now that we've discussed some details on the pathophysiology of this disease and where immunotherapy fits into our management plans, let's turn our attention to another treatment option. The USFDA recently granted orphan drug designation to M7824, which is an investigational, bifunctional fusion protein. Could you explain for us the different parts of the M7824 fusion protein and the mechanism of action?

Dr. Oh:

Yes. As you mentioned, M7824 is a very, very interesting compound. So, you know, the TGF beta is very important immunosuppressive component in tumor microenvironment. So, nowadays, the strategy targeting both immune checkpoint inhibitor component and TGF beta together is ongoing. M7824 is one fusion protein compound which targets both PD-L1 and TGF beta, so a single drug that can target both components.

Dr. Hamid:

As a follow-up, can you describe the phase I clinical data that supported the use of M7824 and why they are so important?

Dr. Oh:

In the phase I clinical trial using M7824 monotherapy in biliary tract cancer has been conducted. In that study, 30 Asian biliary tract cancer patients were enrolled and treated with M7824 monotherapy. The patients were chemorefractory biliary tract cancer, so majority of the enrolled patients were second-line or third-line setting of biliary tract cancer. And among the 30 enrolled patients, the overall response rate was 23% by the investigator assessment and 20% by independent review, so when we consider the 3% of overall response rate of nivolumab monotherapy in this setting and 5% of overall response rate of pembrolizumab monotherapy in this setting, this 20% of overall response rate of M7824 monotherapy is quite encouraging data. And the response duration of M7824 was reported, ranged 8 months to 13.9 months at the time of data cutoff.

And another interesting finding is that in this study, all 4 subtypes of biliary tract cancer were enrolled. That is intrahepatic cholangio, extrahepatic cholangio and gallbladder and ampulla of Vater cancer, and the response was observed across these 4 subtypes. Most interesting finding is that the overall survival in these patients was more than 1 year, 12.7 months. Usually, in the first-line refractory second-line setting, the overall survival of biliary tract cancer is around 5 to 7 months, so second- or third-line setting all together, M7824 monotherapy, the overall survival more than 1 year is quite encouraging data. So, based on this observation, currently there is ongoing phase II study. This study only targets second-line setting of biliary tract cancer and treat the patients with M7824 monotherapy. The study is ongoing nowadays.

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Dr. Hamid:

And just before we wrap up today's conversation, Dr. Oh, are there any other areas you think we should either cover or revisit for our audience?

Dr. Oh:

So, at the very beginning as I mentioned so far, in the biliary tract cancer field, we haven't had very good drugs except gemcitabine/cisplatin combination as a first-line and 5-FU-based chemotherapy as second-line. That's all. So far we haven't had any good targeted agents and we haven't had any good immunotherapy so far even, but as I mentioned, biliary tract cancer has very, very interesting, many genetic subset characteristics which can be targeted with very active, good drugs, so we hope to see the positive research, successful research of targeting this very specific molecular subset of biliary cancer to improve the patient outcome.

And in terms of immunotherapy, yes, this is the start point of the immunotherapy development in biliary tract cancer. So far we have mono agents in the checkpoint inhibitor evidence and we have inhibition evidence and we have efforts to further improve the patient survival with a variety of new strategies like dual-targeting of immune component using M7824 or chemo plus immune checkpoint inhibitor combination.

So, I hope, and I definitely believe, in very near future we will have successes in the drug development in biliary tract cancer and to see the prolongation of the patient survival.

Dr. Hamid:

And thank you for joining me today.

Dr. Oh:

Thank you for having me in this wonderful recording program. It's my pleasure to be here. Thank you.