Advanced Cholangiocarcinoma:
A New Era of Mechanisms and Management

Editor's Note: This is a transcript of an online course released in October 2023. It has been lightly edited for clarity. To obtain credit for participation, CLICK HERE.

Approximately what percent of patients with intrahepatic and extrahepatic cholangiocarcinoma have actionable targets by Next Generation Sequencing?

A. Intrahepatic 0-5%, Extrahepatic 40-50%
B. Intrahepatic 10-20%, Extrahepatic 70-80%
C. Intrahepatic 40-50%, Extrahepatic 10-20%
D. Intrahepatic 70-80%, Extrahepatic 0-5%

The correct for intrahepatic is C

Next Generation Sequencing has really changed the way we think about this disease. There are four different types of biliary tract cancers and we used to normally think about them mainly by where they were located anatomically in the biliary tract. There's intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gall bladder cancer and periampullary cancer and specifically the distinction between intrahepatic and extrahepatic cholangiocarcinoma lies in where these tumors arise in the biliary tree. Intrahepatic cholangiocarcinomas mainly arise beyond the secondary radicals of the tree. For extrahepatic cholangiocarcinoma, this includes perihilar or Klatskins tumors and also distal bile duct tumors.

Getting back specifically to the question, in intrahepatic cholangiocarcinoma, approximately 40 to 50 percent of these tumors have actionable targets and, in extrahepatic cholangiocarcinoma, approximately 10 to 20 percent of these tumors have targets. We'll talk more about what these targets are as the questions progress, but this really highlights the importance of doing molecular profiling for all patients with cholangiocarcinoma.

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Approximately how many cases with cholangiocarcinoma are there in the United States each year?

A. 4,000
B. 8,000
C. 20,000
D. 50,000

The correct answer is B

The answer is 8,000 patients. Just to put that into context, there are about 60,000 cases of pancreas cancer in the U.S. each year, about 150,000 cases of colorectal cancer, about 240,000 cases of lung cancer and about 290,000 cases of breast cancer. Biliary cancers represent about 3 percent of GI cancers and they normally affect patients in their later age, like over 65 or 70 years old, but there's also a shift towards seeing younger patients with cholangiocarcinoma. Interestingly, patients with *FGFR2* fusion-positive tumors, these tumors tend to be in young women. There's a slight predilection in that population.

There's also a variance in the incidence by geography for this tumor. There are much higher rates of cholangiocarcinoma seen in southeast Asia and in the Middle East. In Asia specifically, in China and Thailand are where you see a lot of cholangiocarcinoma. One of the risk factors there is liver flukes which people can pick up by eating raw fish. Some of the other risk factors for cholangiocarcinoma are diseases that cause inflammation to the biliary tree, such as primary sclerosing cholangitis which we see in patients with inflammatory bowel disease, like ulcerative colitis or Crohn's disease. Other risk factors are hepatolithiasis and then also different diseases that cause inflammation of the liver, such as hepatitis B, hepatitis C, fatty liver disease and other conditions that cause cirrhosis. Right now, we

don't have great screening tools for cholangiocarcinoma, but in high-risk populations such as those with primary sclerosing cholangitis, people do often routinely get CA19-9s and liver imaging.

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Based on the FDA approvals in cholangiocarcinoma and tumor agnostic indications, we have approved drugs for which of the following targets?

A. FGFR2 fusions and rearrangements
B. IDH1 mutations and/or BRAF V600E
C. Microsatellite instability-high and deficient mismatch repair protein expression
D. NTRK and/or RET fusions
E. All of the above

The correct answer is all the above

The good news is we have drugs for all of these different targets. For the first two answers here, *FGFR2* fusions and rearrangements and *IDH1* mutations, we have cholangio-specific approvals and, then for the latter three, we have tumor agnostic approvals. For the first two, we're going to talk more about *FGFR* inhibitors, but there are two *FGFR* inhibitors that are approved, pemigatinib and futibatinib. For *IDH1*-mutant tumors, we have ivosidenib. For BRAF V600E-mutant tumors, we have dabrafenib plus trametinib, a combination of BRAF and MEK inhibitors. Then for tumors that have mismatch repair deficiency or that are microsatellite instability-high tumors, we also have immunotherapy, such as pembrolizumab and dostarlimab. Then, NTRK fusions and RET fusions are quite rare in cholangiocarcinoma, seen in less than 1 percent of patients, but we also have several NTRK and RET inhibitors that are available for patients. This again emphasizes the importance of doing molecular profiling for all of our patients with biliary tract cancers.

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What is the approximate median survival for patients with unresectable or metastatic cholangiocarcinoma?

A. 4 months
B. 6 months
C. 8 months
D. 12 months
E. 36 months

The correct answer is D

Here the answer is unfortunately 12 months and we're going to talk about what the treatments are for cholangiocarcinoma in terms of what provides this median overall survival, but overall we do have chemotherapy, immunotherapy and targeted therapy options for our patients, but we're still looking for drugs that are more effective than what we have right now.

In the front line, we think of chemotherapy plus immunotherapy and then, in the second line, if patients have some sort of actionable target in their tumor, we think about targeted therapy, but otherwise we have chemotherapy in the second line.

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What is the current standard of care for patients with treatment-naïve unresectable or metastatic cholangiocarcinoma?

A. Fluorouracil + oxaliplatin (FOLFOX)
B. Gemcitabine + cisplatin + durvalumab
C. Gemcitabine + cisplatin + albumin-bound paclitaxel
D. Regorafenib

The correct answer is B

Here, I'm happy to report that the answer is the combination of gemcitabine, cisplatin and durvalumab and that is after more than a decade of gemcitabine/cisplatin alone being the standard. There are multiple clinical trials where different regimens went up against gemcitabine and cisplatin, but all of them failed to beat this combination. Just recently, there was a phase 3 randomized trial of gemcitabine, cisplatin and durvalumab, which is a checkpoint inhibitor/ a PDL1 inhibitor, compared to gemcitabine/cisplatin. It was a randomized trial and the patients in the triple combination ended up doing better and the primary endpoint was median overall survival and it was 12.8 months in the combination, triple combination arm, and 11.5 months in the chemotherapy-alone arm. One of the most important efficacy endpoints was the 24-month overall survival and this was about 25 percent in the chemo-immunotherapy arm and about 10 percent in the chemotherapy arm. Also, the response rate was a little bit higher in the chemo-immunotherapy arm, 27 percent, compared to 19 percent in the chemotherapy-alone arm.

The grade 3 and 4 toxicity was similar at around 76, 78 percent in the two arms and overall, just a reminder with this regimen, it was people continued the triple combination for six months and then they did durvalumab alone after that as maintenance. This has now become the new standard and durvalumab is now FDA-approved.

There was a question as to how beneficial the durvalumab was, if this was something that was a real signal and so everyone was waiting for the results of the KEYNOTE 966 study which was a combination of gemcitabine, cisplatin, pembrolizumab compared to gemcitabine/cisplatin and this study confirmed the benefit of chemo-immunotherapy in biliary tract cancers where the median overall survival in the chemo-immunotherapy arm was 12.7 months compared to 10.9 months in the chemotherapy-alone arm. Here, the response rate was similar in both groups, but the duration of response was 9.7 months in the chemo-immunotherapy arm and 6.9 months in the chemotherapy arm. There was about a three-month difference in duration of response. Again, the grade 1 and 2 toxicity and grade 3 and 4

toxicity was balanced in both arms. Overall, chemo-immunotherapy has now become the standard front-line therapy. For patients who are not immunotherapy candidates, gemcitabine/cisplatin is also still a reasonable option and also, just as a reminder in terms of how the KEYNOTE 966 regimen was given, in that study gemcitabine/cisplatin could be continued beyond six months.

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Which drug is FDA approved for patients with *IDH1* mutated cholangiocarcinoma who have progressed on 1 or 2 lines of therapy?

A. Ivosidenib
B. Pralsetinib
C. Regorafenib
D. Trastuzumab

The correct answer is A

If you were listening to answers on the previous questions, you'll know the answer to this one is ivosidenib. This is an *IDH1* inhibitor and *IDH1* mutations are seen in approximately 15 to 20 percent of patients with intrahepatic cholangiocarcinoma and probably 1 to 2 percent of patients with extrahepatic cholangiocarcinoma.

The approval for ivosidenib was based on the ClarIDHy study which was a phase 3 study of targeted oral therapy, ivosidenib, compared to placebo and crossover was allowed and it was a 2:1 randomization. The primary endpoint was progression-free survival and in the ivosidenib arm, it was 2.7 months. In the placebo arm, it was 1.4 months with a very positive p value and hazard ratio. You might listen to that and say, oh that's about a one-and-a-half month difference between the two arms, but what was striking was the 6-month and 12-month PFS rate. In the ivosidenib arm, the 6-month PFS rate was 32 percent compared to 0 percent with the placebo arm. The 12-month PFS rate was 22 percent with ivosidenib compared to 0 percent with placebo. There were some patients that really got benefit, some other patients that didn't get that much benefit, but we were happy to see that some people had prolonged stable disease with this combination.

The most common adverse events with this are nausea, diarrhea, fatigue. Some people can have abdominal pain or cough or decreased appetite. Now ivosidenib is approved in patients with *IDH1* mutant cholangiocarcinoma who've had progression on one or two lines of prior therapy.

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Pemigatinib and futibatinib have gained conditional FDA approval for advanced refractory cholangiocarcinoma harboring which target?

A. Any *FGFR2* alteration
B. *FGFR2* amplifications
C. *FGFR2* fusions and rearrangements
D. *FGFR2* mutations

The correct answer is C

Again, this is echoing an answer from a previous question. The answer is *FGFR2* fusions and rearrangements.

And we highlight this because when you see the molecular profiling report from different companies or from your internal molecular profiling platform at your institution, we see all of these different types of alterations. We sometimes see *FGFR2* amplification, we sometimes and commonly see *FGFR2* mutations, but this indication is specifically in patients who have FGFR2 fusions or rearrangement-positive tumors. The fusions and rearrangements are seen in about 10 to 15 percent of patients with intrahepatic cholangiocarcinoma and rarely seen in extrahepatic cholangiocarcinoma. *FGFR2* mutations are seen in about 4 to 5 percent of intrahepatic cholangiocarcinomas and amplifications are probably seen in about 1 to 2 percent of intrahepatic cholangiocarcinomas.

It's really the fusions and rearrangements that we are looking to target.

Just to share the data for pemigatinib and futibatinib, these were both drugs that were studied in non-randomized settings of about 100 patients each where all the patients had fusion-positive cholangiocarcinoma and they were all treated with pemigatinib or futibatinib. For pemigatinib, it was the FIGHT-202 study, a phase 2 study where the overall response rate was 35.5 percent and that was the primary endpoint. The progression free survival was seven months. Then for futibatinib, it was the FOENIX-CCA2 study, another phase 2 study, and there the overall response rate was 42 percent and the PFS was nine months.

A key difference between these two drugs is that pemigatinib is a reversible inhibitor and futibatinib is an irreversible inhibitor. Two drugs that are effective in this population. Futibatinib has been shown in preclinical studies to overcome some of the resistance mutations we sometimes see with earlier generation inhibitors. We know that resistance can develop due to mutations in the kinase domain of *FGFR2* and some think that potentially the prolonged duration of response and PFS and possibly even the ORR is related to futibatinib's additional action against some of these resistance mutations that we see in other drugs. So again, really important to do molecular profiling in patients with cholangiocarcinoma so we can test for all these targets that we now have approved drugs for.

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What are key class specific toxicities of *FGFR* inhibitors?

A. Central serous retinopathy/dry eyes
B. Dry mouth/stomatitis
C. Hyperphosphatemia
D. Nail disorders and Palmar-plantar erythrodysesthesia
E. All of the above

The correct answer is all the above

The answer is all of these different side effects, to be honest, but actually if we're proactive about them and monitor them, we can do a good job of keeping people's quality of life good and we can minimize the chance of these becoming grade 3/grade 4, again if we do a lot of good supportive care.

Let's talk about each of these because it's important to know about them if we put patients on *FGFR* inhibitors. Central serous retinopathy is also the same as retinal detachment. This is seen in about 7 to 10 percent, 7 to 12 percent of patients that go on these *FGFR* inhibitors. It's really important that ophthalmology is following these patients and the way this manifests is patients sometimes say "I'm having some floaters, I'm seeing some halos, I'm seeing some stars in my vision" and, as soon as I hear that, I ask patients to stop the drug, the *FGFR* inhibitor that they're on, and I send them to ophthalmology. The vast majority of these patients that have retinal toxicity is, most of the time it's grade 1/grade 2 and usually by stopping the drug for a couple of days, the symptoms resolve. You can often restart at the same dose. If it was more severe, then I would, you know, go at a lower dose, but otherwise with dose adjustments and dose holds, this usually goes away and almost never see any kind of permanent or significant detriment in visual function.

The other eye toxicities sometimes people have is they can have dry eyes which is usually common, so people use eye drops. They can sometimes have blurry vision or they can sometimes, as a late side effect, get cataracts. As ophthalmology is following these patients, that's important to look for.

The second one, dry mouth and stomatitis. The dry mouth is very common. People sometimes use the artificial saliva or keep hydration options near them during the day. Stomatitis, most of the time people, this is going to be grade 1/grade 2, but sometimes it can be grade 3. You know, using salt water or baking soda rinses can help in the early stages. Using dexamethasone mouthwashes or other steroid mouthwashes can be helpful if it's more severe. Hyperphosphatemia, this is seen because we're trying to hit *FGFR2* because we're seeing *FGFR2* fusions, but these are *FGFR1-3* or *FGFR1-4* inhibitors and so when you hit *FGFR1*, it's an on-target off-tumor side effect where you hold onto your phosphorus in your kidneys and also in your gut. Hyperphosphatemia is seen in a high percentage of patients who go on these *FGFR* inhibitors, but with using phosphorus binders or drugs that have you urinate out phosphorus, having people stay well-hydrated, have people move their bowels and sometimes even having a low phosphorus diet, all of these can help with hyperphosphatemia.

And then nail disorders. People can sometimes have nail infections, like paronychia, or they can have cracking or breaking of the nails. Certainly, discoloration. They can have nail lifting. Sometimes their nails fall off. We watch this closely and have people see podiatry as needed. Sometimes people can also get palmar plantar erythrodysesthesia or hand-foot syndrome on their hands and feet. People have seen this with other tyrosine kinase inhibitors and also with capecitabine in oncology. This is something that's very much worth intervening upon early with the usual 40 percent urea, different emollients and if it gets worse, like chronic grade 2 even, we often send these patients to dermatology.

Overall, a series of different side effects with these *FGFR* inhibitors, but having awareness of them and asking patients to be proactive with supportive care can help people have good quality of life and maintain patients on full dose or at least just one dose reduction of these different drugs.

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Which exam is important to obtain before initiating *FGFR* inhibitors?

A. Dual x-ray absorptiometry scan
B. Echocardiogram
C. Ophthalmic exam
D. Pulmonary function tests

The correct answer is C

The answer is an ophthalmic exam and this eye exam, we do at baseline because of the concern of the central serous retinopathy or retinal detachment. We get this study at baseline to make sure people have no major eye issues before they start and then I normally get eye exams if people develop symptoms. If they have new floaters or new halos that they're seeing, for example, in their vision, new blurry vision, that's when I often send them back to ophtho. Then, of course, because people can develop cataracts, it's also helpful to have ophthalmology on board. That is an important exam to get before they start.

There isn't a significant amount of cardiac toxicity usually with *FGFR* inhibitors, so I do not get a baseline echocardiogram. For PFTs, also not a significant amount of lung toxicity with this regimen. We do see patients developing bone metastases sometimes in the setting of cholangiocarcinoma, but *FGFR* inhibitors don't generally affect bone density. DEXA scans are also not required before starting these drugs.

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What is the main cardiac toxicity concern with ivosidenib?

A. Atrial fibrillation
B. Heart failure
C. Hypertension
D. QTc prolongation

The correct answer is D

The answer to this one is QTc prolongation. For patients going on ivosidenib, we get a baseline EKG and we follow the EKG while they're on treatment. In the ClarIDHy study which, as I mentioned, is the phase 3 study that led to the approval of ivosidenib, 12 patients or 10 percent of patients developed QTc prolongation with ivosidenib compared to two patients or 3 percent in the placebo arm. Five of the 12 patients needed dose reductions of ivosidenib due to QTc prolongation.

The key things to look out for are the medications you're co-administering with ivosidenib. If patients are taking drugs that already increase the QTc interval, so for example Zofran is a drug we sometimes give for nausea, that can increase the risk of QTc prolongation. Then also drugs that interact with ivosidenib, such as moderate or

strong CYP3A4 inhibitors. In terms of other cardiac toxicities with ivosidenib, we also saw hypertension in 5 percent vs. 4 percent of patients in terms of ivosidenib vs. placebo. Not significantly more than placebo. Less likely related in my mind.

Overall, it's something to look out for. If patients have congenital long QTc syndrome or congestive heart failure, if they have underlying electrolyte abnormalities or, again, if they're on certain drugs that may interact with ivosidenib, certainly it's important to watch these patients closely. But overall, ivosidenib is a well-tolerated drug and certainly a great option for patients with *IDH1*-mutant tumors.

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