Transcript Details
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Cholangiocarcinoma: Treatment with Targeted Therapies

ReachMD Announcer:
Welcome to *Project Oncology* on ReachMD.

This medical industry feature, titled "Cholangiocarcinoma: Treatment with Targeted Therapies," is sponsored by Incyte.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Cholangiocarcinoma is a rare and aggressive form of cancer affecting the bile ducts that poses significant challenges in diagnosis and treatment. So when chemotherapy and other first-line therapies are unsuccessful, what are our other options for patients battling this disease?

This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to discuss targeted therapies for cholangiocarcinoma is Dr. Amit Mahipal, who is a Professor of Medicine at Case Western Reserve University and the Gastrointestinal Oncology Program Leader at Seidman Cancer Center and Case Western Reserve University.

Dr. Mahipal, welcome to the program.

Dr. Mahipal:
Thank you for having me, Dr. Caudle.

Dr. Caudle:
Well, we're excited that you're here. So, let's start off with an overview of cholangiocarcinoma. Dr. Mahipal, what can you tell us about this condition?

Dr. Mahipal:
Well, as you alluded to earlier, cholangiocarcinoma, or CCA for short, is a rare form of cancer that develops within the thin bile ducts that connect the liver, gallbladder, and small intestine. These ducts carry bile that's made in the liver to help break down and digest fatty foods.[1]

Now there are a few different subtypes of CCA depending on the location of the tumor,[2,3] but specifically, incidence of intrahepatic CCA —or iCCA—which affects the bile ducts inside the liver, has been increasing over the years.[3]

CCA can be difficult to diagnose because many patients are either asymptomatic or have non-specific symptoms, so it's often diagnosed late when the prognosis is poor.[2,3] When symptoms do appear, patients may present with jaundice, pruritus, steatorrhea, dark urine, abdominal pain, weight loss, fever, and/or nausea and vomiting.[4]

While standard surgical resection can be curative, only 30 to 40 percent of patients are eligible, and recurrence after resection can happen in up to 50-60 percent of patients.[5-7]

Dr. Caudle:
Thank you for that overview, Dr. Mahipal. Now, you mentioned that CCA is not easy to diagnose given the nature of peoples' symptoms. Based on the treatment options available, how can we develop tailored treatment plans for patients diagnosed with CCA?

Dr. Mahipal:
So, if you take a look at the available treatment options first, we have surgical resection like I mentioned earlier, but we also have standard treatments like locoregional therapy, liver transplant for iCCA patients with cirrhosis, or chemotherapy. And on that last note, first and second-line chemotherapy have varying degrees of success in improving outcomes for patients with CCA.[2]

So, in an effort to improve outcomes and the prognosis for these patients, we need to understand CCA at a molecular level, along with its risk factors, morbidity factors, and mechanism of action for various treatments to build a tailored care plan for each patient.[2]

And that's where biomarker testing comes into play. Investigators have been conducting research for more than a decade to identify a molecular map to develop targeted therapies for CCA.[2]

In fact, up to 50 percent of patients with iCCA may have actionable genomic alterations.

Dr. Caudle:
Can you elaborate on these genomic alterations? Are there any that show promise for iCCA treatment?

Dr. Mahipal:
Yes, we now know through molecular profiling that fibroblast growth factor receptor 2 fusions and rearrangements, or FGFR2 for short, are some of the most common genomic alterations, showing up in 10 to 16 percent of patients with iCCA.[2]

The good news is that even though FGFR2 fusions are key drivers of tumor growth, they're detectable early in disease progression,[8] making early testing and detection key in diagnosis and informing treatment plans.[2]

Because of the important role it can play, the NCCN clinical practice guidelines recommend molecular testing for patients living with unresectable or metastatic CCA.[9]

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle and today I'm speaking with Dr. Amit Mahipal about the role of biomarker testing in the diagnosis and treatment of cholangiocarcinoma.

So, Dr. Mahipal, we spoke a bit earlier about how the identification of FGFR2 fusions and rearrangements through molecular testing have the potential to inform iCCA treatment options. So, have you seen any new developments in the past few years?

Dr. Mahipal:
I have. In 2020, the FDA approved pemigatinib—also known as Pemazyre—as the first kinase inhibitor indicated for adults with previously treated, unresectable, locally advanced or metastatic CCA with an FGFR2 fusion or other rearrangement as detected by an FDA-approved test.

This indication received an accelerated approval based on overall response rate and duration of response. And continued approval for this indication may depend on verification and description of clinical benefit in a subsequent confirmatory trial or trials.[10] Since its approval, Pemazyre has over three years of clinical use with over 1,000 patients treated.[10]

Now it's important to keep in mind that FGFR2 fusions are found almost exclusively in iCCA. And when they occur, they can cause constitutive FGFR2 signaling, which contributes to a variety of tumorigenic processes. But Pemazyre inhibits FGFR2 signaling, which may decrease tumor cell proliferation and survival in FGFR-driven tumors.[11]

Dr. Caudle:
Well, this sounds like an interesting option for these patients. But before we continue, let's pause for some important safety information.

ReachMD Announcer:
PEMAZYRE® (pemigatinib) is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

PEMAZYRE can cause serious adverse reactions including Ocular Toxicity (Retinal Pigment Epithelial Detachment [RPED] and Dry Eye), Hyperphosphatemia and Soft Tissue Mineralization, and Embryo-Fetal Toxicity.

See additional Important Safety Information at the end of this program.

Dr. Caudle:
Now continuing with our discussion, Dr. Mahipal, what clinical trial data do we have that supported Pemazyre's FDA approval?

Dr. Mahipal:
We have some positive data based on the FIGHT-202 multicenter, open-label, single-arm clinical trial. In 107 patients with locally advanced or metastatic CCA that had progressed on or after at least one prior therapy and who had an FGFR2 fusion or non-fusion rearrangement, Pemazyre demonstrated a 36 percent objective response rate, a median duration of response of 9.1 months.[12]

Dr. Caudle:
What additional data do we have for Pemazyre?

Dr. Mahipal:
Results for additional endpoints include a median progression-free survival of 6.9 months, 82% disease control rate, and a median overall survival of 21.1 months. OS data were not mature; a total of 40 patients (37%) had died. Due to potential variability in the natural history of CCA, this single-arm study may not adequately characterize these additional endpoints.[12]

The most common adverse reactions, with incidence of greater than or equal to 20 percent in all patients, were hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin.[12]

Dr. Caudle:
Thanks for sharing that data with us, Dr. Mahipal. Now we've covered a lot of ground, but before we close, is there anything else you'd like to leave with our audience today?

Dr. Mahipal:
Pemazyre has been approved for nearly 4 years with over 1,000 patients treated. Based on clinical trial data, this patient population has an option in Pemazyre to help manage their CCA when first-line treatments have failed to provide meaningful results.[10,12]

Dr. Caudle:
For ReachMD, I'm Dr. Jennifer Caudle. Let's now review the full important safety information.

ReachMD Announcer:
Important Safety Information

Ocular Toxicity
Retinal Pigment Epithelial Detachment (RPED): PEMAZYRE can cause RPED, which may cause symptoms such as blurred vision, visual floaters, or photopsia. Clinical trials of PEMAZYRE did not conduct routine monitoring including optical coherence tomography (OCT) to detect asymptomatic RPED; therefore, the incidence of asymptomatic RPED with PEMAZYRE is unknown.

Among 635 patients who received a starting dose of PEMAZYRE 13.5 mg across clinical trials, RPED occurred in 11% of patients, including Grade 3-4 RPED in 1.3%. The median time to first onset of RPED was 56 days. RPED led to dose interruption of PEMAZYRE in 3.1% of patients, and dose reduction and permanent discontinuation in 1.3% and in 0.2% of patients, respectively. RPED resolved or improved to Grade 1 levels in 76% of patients who required dosage modification of PEMAZYRE for RPED.

Perform a comprehensive ophthalmological examination including OCT prior to initiation of PEMAZYRE and every 2 months for the first 6 months and every 3 months thereafter during treatment. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of PEMAZYRE. Modify the dose or permanently discontinue PEMAZYRE as recommended in the prescribing information for PEMAZYRE.

Dry Eye: Among 635 patients who received a starting dose of PEMAZYRE 13.5 mg across clinical trials, dry eye occurred in 31% of patients, including Grade 3-4 in 1.6% of patients. Treat patients with ocular demulcents as needed.

Hyperphosphatemia and Soft Tissue Mineralization
PEMAZYRE can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcification, calcinosis, and non-uremic calciphylaxis. Increases in phosphate levels are a pharmacodynamic effect of PEMAZYRE. Among 635 patients who received a starting dose of PEMAZYRE 13.5 mg across clinical trials, hyperphosphatemia was reported in 93% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range 1-169). Phosphate lowering therapy was required in 33% of patients receiving PEMAZYRE.

Monitor for hyperphosphatemia and initiate a low phosphate diet when serum phosphate level is >5.5 mg/dL. For serum phosphate levels >7 mg/dL, initiate phosphate lowering therapy and withhold, reduce the dose, or permanently discontinue PEMAZYRE based on duration and severity of hyperphosphatemia as recommended in the prescribing information.

Embryo-Fetal Toxicity
Based on findings in an animal study and its mechanism of action, PEMAZYRE can cause fetal harm when administered to a pregnant woman. Oral administration of pemigatinib to pregnant rats during the period of organogenesis caused fetal malformations, fetal growth retardation, and embryo-fetal death at maternal exposures lower than the human exposure based on area under the curve (AUC) at the clinical dose of 13.5 mg.

Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the last dose.

Adverse Reactions: Cholangiocarcinoma
Serious adverse reactions occurred in 45% of patients receiving PEMAZYRE (n=146). Serious adverse reactions in ≥2% of patients who received PEMAZYRE included abdominal pain, pyrexia, cholangitis, pleural effusion, acute kidney injury, cholangitis infective, failure to thrive, hypercalcemia, hyponatremia, small intestinal obstruction, and urinary tract infection. Fatal adverse reactions occurred in 4.1% of patients, including failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion.

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received PEMAZYRE. Adverse reactions requiring permanent discontinuation in ≥1% of patients included intestinal obstruction and acute kidney injury.

Dosage interruptions due to an adverse reaction occurred in 43% of patients who received PEMAZYRE. Adverse reactions requiring dosage interruption in ≥1% of patients included stomatitis, palmar-plantar erythrodysesthesia syndrome, arthralgia, fatigue, abdominal pain, AST increased, asthenia, pyrexia, ALT increased, cholangitis, small intestinal obstruction, alkaline phosphatase increased, diarrhea, hyperbilirubinemia, electrocardiogram QT prolonged, decreased appetite, dehydration, hypercalcemia, hyperphosphatemia, hypophosphatemia, back pain, pain in extremity, syncope, acute kidney injury, onychomadesis, and hypotension.

Dose reductions due to an adverse reaction occurred in 14% of patients who received PEMAZYRE. Adverse reactions requiring dosage reductions in ≥1% of patients who received PEMAZYRE included stomatitis, arthralgia, palmar-plantar erythrodysesthesia syndrome, asthenia, and onychomadesis.

Clinically relevant adverse reactions occurring in ≤10% of patients included fractures (2.1%). In all patients treated with pemigatinib, 0.5% experienced pathologic fractures (which included patients with and without cholangiocarcinoma [N = 635]). Soft tissue mineralization, including cutaneous calcification, calcinosis, and non-uremic calciphylaxis associated with hyperphosphatemia were observed with PEMAZYRE treatment.

Within the first 21-day cycle of PEMAZYRE dosing, serum creatinine increased (mean increase of 0.2 mg/dL) and reached steady state by Day 8, and then decreased during the 7 days off therapy. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

In cholangiocarcinoma (n=146) the most common adverse reactions (incidence ≥20%) were hyperphosphatemia (60%), alopecia (49%), diarrhea (47%), nail toxicity (43%), fatigue (42%), dysgeusia (40%), nausea (40%), constipation (35%), stomatitis (35%), dry eye (35%), dry mouth (34%), decreased appetite (33%), vomiting (27%), arthralgia (25%), abdominal pain (23%), hypophosphatemia (23%), back pain (20%), and dry skin (20%).

Drug Interactions
Avoid concomitant use of strong and moderate CYP3A inhibitors with PEMAZYRE. Reduce the dose of PEMAZYRE if concomitant use with a strong or moderate CYP3A inhibitor cannot be avoided. Avoid concomitant use of strong and moderate CYP3A inducers with PEMAZYRE.

Special Populations
Advise lactating women not to breastfeed during treatment with PEMAZYRE and for 1 week after the last dose.

Reduce the recommended dose of PEMAZYRE for patients with severe renal impairment as described in the prescribing information.

Reduce the recommended dose of PEMAZYRE for patients with severe hepatic impairment as described in the prescribing information.

Please see Full Prescribing Information for PEMAZYRE.

Dr. Caudle:
Those are great comments for us to think on as we consider options for appropriate CCA patients. And I'd like to thank my guest, Dr. Mahipal, for helping us better understand the benefits and risks of Pemazyre when treating CCA. Dr. Mahipal, it was great speaking with you today.

Dr. Mahipal:
Thanks again for having me.

ReachMD Announcer:
This program was sponsored by Incyte and Dr. Mahipal has been compensated by Incyte for his time. If you missed any part of this discussion, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge.

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