

BEST PRACTICES in Managing FGFRi Treatment–Related AEs: Intrahepatic Cholangiocarcinoma

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CHOLANGIOCARCINOMA is the second most common liver tumor. The intrahepatic subgroup, the least frequently seen form, accounts for about 10% of these tumors and affects about 8000 people per year in the United States. Until recently, the overall 5-year survival rate was 15% to 20%; less than 5% of those with metastatic disease survived for 5 years.¹ First-line treatment typically includes chemotherapy with gemcitabine and cisplatin, and a commonly used second-line treatment includes FOLFOX (fluorouracil, leucovorin, and oxaliplatin). However, there is limited efficacy with this approach; an objective response rate (ORR) of 5% and a median overall survival (OS) rate of 6.2 months have been demonstrated.²

There have been significant advances in the treatment options for intrahepatic cholangiocarcinoma over the last 5 to 10 years based on the recognition that fusions or rearrangements of the fibroblast growth factor receptor (FGFR), and especially of FGFR2, play an important role in about 10% to 16% of intrahepatic cholangiocarcinomas.³

Approved FGFR2 inhibitors (FGFRi) for second-line treatment of advanced cholangiocarcinoma with FGFR2 fusions or rearrangements include pemigatinib and futibatinib.^{4,5} Pemigatinib, which was approved first, is given orally on a 14-days-on, 7-days-off schedule; its use has resulted in an ORR of 35.5% and progression-free survival (PFS) of 7.5 months.^{3,4} Futibatinib, given daily, resulted in an ORR of 42% and PFS of 9 months in clinical trials; it was also demonstrated that it may be able to overcome some of the resistance mutations seen after treatment with other FGFRi.²

Common Adverse Events

Patients must be made aware that all FGFRi are associated with adverse events (AEs) and that early recognition and notification about any AEs to their health care providers are essential. In contrast to chemotherapy, with which the patient feels bad for a few days afterward, FGFRi are given orally over prolonged periods; thus, AEs can occur even months after initiation of therapy. However, most of these AEs are grade 1 and 2 and can generally

be managed in the outpatient setting. The **Table** shows the frequency of common FGFRi AEs.⁴⁻⁶

This publication presents key takeaways of best practices in the management of FGFRi AEs for patients with intrahepatic cholangiocarcinoma, as identified by an *OncLive* Insights program panel that was moderated by **Lipika Goyal, MD**, and included **R. Katie Kelley, MD**; **Caroline Kuhlman, NP**; and **Chaundra Bishop**, a patient with intrahepatic cholangiocarcinoma.

The AE profiles, with a few exceptions, are similar for both drugs, and treatment with FGFRi is generally well tolerated. Although most AEs are low grade, some of them might have an impact on quality of life either because of their chronicity or the need for additional interventions to manage them. In the FIGHT-202 trial (NCT02924376), which evaluated pemigatinib, only 9% of patients discontinued treatment due to AEs, and 14% needed dose reductions, even though serious AEs were experienced by 45% of patients.³ In the FOENIX-CCA2 trial (NCT02052778), which evaluated futibatinib, 99% of

Table.
Common Adverse Events With Use of Approved FGFR Inhibitors²⁻⁶

Adverse effect	Frequency, all grades	Frequency, grade ≥ 3
Hyperphosphatemia	60.0%-85.0%	0%-30.0%
Hypophosphatemia	0%-23.0%	0%-12.0%
Increased creatinine	41.0%-58.0%	0%-1.4%
Stomatitis	30.0%-35.0%	5.0%-6.0%
Dry mouth	34.0%-35.0%	—
Dysgeusia	25.0%-40.0%	—
Alopecia	34.0%-49.0%	—
Nail toxicity	43.0%-47.0%	1.9%-2.1%
Dry skin	20.0%-29.0%	0%-0.7%
Dry eye	25.0%-35.0%	0.7%-1.0%
Palmar-plantar erythrodysesthesia syndrome	15.0%-21.0%	4.1%-4.9%
Diarrhea	39.0%-47.0%	1.0%-2.7%
Constipation	35.0%-39.0%	0%-0.7%
Nausea	24.0%-40.0%	1.9%-2.1%
Fatigue	37.0%-42.0%	4.8%-8.0%
Arthralgia	25.0%	0%-6.0%
Decreased hemoglobin	43.0%-52.0%	6.0%
Decreased platelets	28.0%-42.0%	1.0%-3.4%
Decreased leukocytes	18.0%-33.0%	1.1%-1.4%
Increased alanine aminotransferase	43.0%-50.0%	4.1%-7.0%

patients experienced at least 1 AE. Serious treatment-related AEs were reported in 10 patients (10%) treated with futibatinib. Dose interruptions or reductions were necessary in 50% and 54% of patients, respectively, but only 2% of patients discontinued the drug permanently due to AEs.²

Hyperphosphatemia is one of the most common AEs. The currently approved drugs are pan-FGFR inhibitors targeting FGFR1, FGFR2, FGFR3, and FGFR4. An on-target but off-tumor effect is the inhibition of FGFR1, which impacts the ability of the kidneys to remove phosphorus, leading to more

retention in the gut.^{2,3} The panelists noted that hyperphosphatemia is seen more frequently and with higher severity in patients using futibatinib, which may be partly explained by its continuous dosing versus pemigatinib, which has a discontinuous administration schedule. Hypophosphatemia may be a result of the attempt to treat hyperphosphatemia. The panelists noted that there is a risk of calcium and phosphorous deposition in different organs that they have not observed but that has been reported.⁷

Nearly 40% of patients may experience constipation, probably due to the

disturbed phosphate metabolism, but diarrhea is also seen and believed to be due to FGFR4 inhibition, according to the panelists. Other gastrointestinal symptoms may include stomatitis, loss of appetite, nausea, and weight loss.^{2,3}

Skin and nail toxicities, including alopecia and dry skin, are quite common as is hand-foot syndrome (PPES) of the fingers and toes that is manifested by calluses, hyperkeratosis, erythema, and fissures. Brittle or discolored nails, paronychia, onychomadesis (shedding of the peripheral part of nails), and onycholysis (separation of the nail from nail bed) have been described.^{2,3,7} The health care practitioners on the panel noted that based on what they have seen in their practices, nail toxicities may be underreported.

Potentially serious AEs that may be seen in a small number of patients include different forms of ocular toxicity. Blurry vision may occur due to dry eyes or retinal pigment epithelial detachment (RPED). Onset of any visual symptoms or AEs requires referral to an ophthalmologist.^{4,5}

The panelists agreed that most patients can tolerate treatment with FGFRi and do well on them, but being well informed and proactive about AE symptom management is essential for best outcomes.

Management of AEs Associated With FGFRi Use

It is imperative to counsel patients about potential AEs before they start treatment with FGFRi. The panelists cautioned that because these oral agents can be taken at home, patients may think they will be easier to tolerate than chemotherapy, so it is important to make patients aware of potential FGFRi treatment-related AEs.

Additionally, patients should be informed that severe infections or hospitalizations due to FGFRi treatment are rare. Many patients experience AEs, because they may continue treatment for months or even years; FGFRi work well and cause dramatic tumor shrinkage and prolongation of PFS.

Patients should be educated about the potential for ocular toxicities (changes in vision, blurred vision), mucositis, dry mouth, alopecia, skin and nail changes, bowel changes, and electrolyte abnormalities with hyperphosphatemia. They need to be encouraged to contact their care team as soon as they observe new symptoms, but they can also be reassured that severe infections or hospitalizations are rare. Regular monitoring is recommended at least every 2 to 3 months and more frequently if certain AEs occur. Below are practical tips for managing AEs associated with FGFRi treatment.

Hyperphosphatemia

The median time to onset of hyperphosphatemia has been demonstrated to be 5 to 8 days.^{4,5} Serum phosphorus levels should be checked 1 to 2 weeks after treatment initiation, and therapy with a phosphorus-binding agent is generally implemented at a level of at least 5.5 mg/dL. If the level does not drop below 7 mg/dL after 2 weeks, the FGFRi is held until normalization, and the dose is lowered if this is a repeat occurrence.^{4,5} The oncologists on the panel indicated that because there is a risk for resistance developing if the FGFRi dose is lowered, they prefer to treat the hyperphosphatemia aggressively versus lowering doses whenever possible. Patients generally tolerate phosphorus binders well, but compli-

ance may be difficult, since they must take multiple pills every time they eat. Patients should be counseled to take the pills when they eat meals or snacks and to skip the medication if they skip a meal. Additionally, if a patient has a week off of their FGFRi treatment, they should not take the phosphorus binder. Although a low-phosphorus diet is indicated as guidance for patients with high phosphorus levels, the efficacy is limited, and adherence is difficult due to its impact on quality of life.

Ocular Toxicities

Patients should have a baseline ophthalmologic examination that includes optical coherence tomography; they should be monitored every 2 to 3 months and be seen at the onset of any ocular symptoms. Most ocular AEs resolve but can significantly impact quality of life.

Blurred vision may be caused by RPED with a median onset of 40 to 56 days after treatment begins; it requires an urgent referral to an ophthalmologist. If symptoms do not resolve or worsen, dose reductions or holds may be necessary.^{4,5}

Many patients experience dry eye; artificial tears eye drops should be recommended to all patients beginning treatment. If severe, this can majorly impact a patient's quality of life. Prolific eyelash growth (trichiasis) is another potential AE. Eyelashes may grow inward and cause abrasions; patients may need to see an ophthalmologist to have them regularly epilated.

Nail and Skin Toxicities

Most patients will experience some nail toxicity, but their frequency is likely underreported by patients.

Furthermore, the panelists noted, most oncologists do not know how to deal with nail toxicities and how to educate patients about preventive strategies. Education about the likelihood of nail toxicities is essential, the panelists agreed, because they can cause physical pain and also be visibly alarming for patients. Nail changes typically start with thickening or ridging, then a greater part of the nail becomes white and slowly becomes detached from the nail bed. Patients should be educated about these potential AEs and be informed that many of these changes will be experienced during the first 3 to 6 months of treatment. The patient panelist also noted that educational materials with potential prevention strategies for these AEs would be beneficial. Mitigation techniques include keeping the nails clean and sterile »

The Cholangiocarcinoma Foundation



Founded in 2006, the Cholangiocarcinoma Foundation's (CCF's) mission is to find a cure and improve the quality of life for those affected by cholangiocarcinoma. The CCF's 2024 Annual Conference, which includes a day for patients and caregivers as well as 2 days for the medical and scientific community, will be held April 17-19, 2024, at the Salt Palace Convention Center in Salt Lake City, Utah.

To learn more about CCF or about the conference, visit <https://cholangiocarcinoma.org>.

by applying vinegar soaks or a topical antimicrobial agent. Infections should be treated with an antibacterial agent; in the case of paronychia, the patient should be referred to a dermatologist.

Dry skin should be managed with the application of thick moisturizers containing lanolin. If PPES develops, the patient should be advised to use cold or tepid water for showers and baths and when washing dishes. Keratolytic agents that contain 40% urea and/or salicylic acid can be used to exfoliate hyperkeratotic calluses, and the affected areas should be cushioned with gel inserts or the use of soft shoes. In severe cases, use of cortisone creams or topical antibiotics may be indicated.⁶

Gastrointestinal AEs

Stomatitis is a common symptom that significantly affects patients' quality of life, because it impacts how they eat and drink. Patients should be counseled to complete any needed dental work before initiating FGFRi treatment. Other preventive strategies include frequent mouth washing (3 or more times per day) to reduce bacteria in the mouth, rinsing with a mixture of baking soda and water, and brushing with a soft toothbrush using mild toothpaste. Patients should also be told to avoid very spicy, salty, or citrus-based foods, and they may want to avoid very hot drinks and foods to avoid burns. For patients who do experience mouth sores, coating agents may be helpful. The topically applied preparation known as *magic mouthwash* includes antacid coating agents and analgesics that help mitigate the discomfort.⁶

Dry mouth can also have a significant impact on quality of life. Preventive strategies include maintaining

hydration and drinking fluids while eating. Patients may also want to use soluble lubricants that are available as a mouth rinse or toothpaste.

Diarrhea can usually be treated with loperamide, which is available over the counter, or atropine/diphenoxylate, which requires a prescription.

Conclusion

Preventive measures combined with regular monitoring allow most patients to continue treatment with their FGFRi with limited need for dose holds or reductions. Patients should be encouraged to call their care team about any AE that impacts their ability to function normally. If a patient develops a fever, severe vision changes, or intractable diarrhea or anything that is significantly limiting, they should be instructed to seek care immediately. The patient panelist emphasized the need for up-front counseling with specific information about what AEs to expect, when they may occur, and how they may be prevented. Care teams should explore opportunities to share this information in patient counseling and educational materials and emphasize that they are available to help manage AEs so patients can enjoy a good quality of life. ■

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Learn more by watching the full video series *FGFR Inhibitors: Best Practices in Managing Treatment and Treatment-Related Adverse Events*, at [Onclive.com](https://www.onclive.com).