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Positive Quality Intervention: Futibatinib (Lytgobi®) Adverse Effects and Supportive Care Management

Description: The Fibroblast Growth Factor Receptor (FGFR) pathway plays a key role in multiple fundamental cellular processes. The FGFR inhibitor futibatinib (Lytgobi®) is approved for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements.[1] The FGFR inhibitor drug class carries specific adverse effect profiles and monitoring considerations. The purpose of this PQI is to outline adverse effects of futibatinib (Lytgobi®) and provide recommendations to educate, monitor, and support patients appropriately.

Background: The FGFR receptor belongs to a family of transmembrane tyrosine kinases. There are 4 known transmembrane receptors, FGFR 1 to 4, that when stimulated, lead to activation of downstream signaling pathways resulting in oncogenic cell proliferation, survival, migration, and differentiation.[2] Genomic FGFR alterations occur in 5-10% of all human cancers, with an increase in frequency of 10-30% in urothelial carcinoma and intrahepatic cholangiocarcinoma.[2] As these novel therapies are researched in clinical trials, a specific side effect profile has emerged across the FGFR inhibitor drug class including hyperphosphatemia, diarrhea, fatigue, ocular toxicity, and dermatologic toxicity.[3] It is known that FGFR1 regulates phosphate homeostasis, and therefore a direct result of FGFR inhibition is hyperphosphatemia.[3] Management of hyperphosphatemia depends on the serum phosphate levels and should be assessed at baseline, one week after initiation of therapy, at the end of the first cycle, and regularly throughout treatment.[3] Patient education on foods containing phosphorus is necessary and phosphorus-lowering therapy may be needed to initiate with FGFR inhibitors. Diarrhea is also a known and common side effect of this drug class, and it is recommended that patients be advised to obtain loperamide at time of initiation of a FGFR inhibitor and counseled on appropriate administration.[3] Ocular toxicity may arise in the form of dry eye and can progress to more serious effects such as retinal detachment. Ophthalmological exam should be performed prior to treatment.[3] Finally, FGFR inhibitors carry risk of various dermatological toxicities such as stomatitis, dry skin, Palmar-Plantar Erythrodysesthesia Syndrome (PPES), and nail toxicities.[3] It is important that members of the healthcare team are aware of these adverse events to allow for proper patient education regarding what to expect, and how to proactively manage and prevent toxicity. This can prevent premature drug discontinuation while maintaining quality of life. Applied recommendations can help patient's adherence and persistence on futibatinib, which can lead to better clinical outcomes as an ultimate goal of therapy. It is important that the multidisciplinary team be involved in the management of these patients to continuously assess tolerability and the need for additional supportive care options.

PQI Process: Upon receipt of an order for an FGFR inhibitor

- Review patient's history, including diagnosis and prior treatments and verify the presence of a susceptible FGFR2 fusion or other rearrangements
- Ensure ophthalmological examination (including OCT of macula) completed prior to initiation
- Assess baseline renal and hepatic function and need for any initial dose reductions
- Avoid coadministration with dual P-gp and Strong CYP3A inducers/inhibitors
- Recommended dose 20 mg (five 4 mg tablets) by mouth once daily with or without food
- Evaluate pregnancy status prior to use in females of reproductive potential
    - Counsel females and males with female partners of reproductive potential on appropriate contraception due to risk of fetal harm

- Recommend supportive care options – generic if applicable to decrease financial toxicity

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) Sheet
- Counsel patients on ocular toxicity, exams, and management
- Hyperphosphatemia Recommendations
    - Provide education on signs and symptoms of hyperphosphatemia (muscle cramps, numbness/tingling around the mouth)[1]
    - Obtain phosphate levels check at baseline and monitoring throughout treatment
        - Phosphate lowering drugs should be discussed with treating physician for patients with elevated phosphorus levels
    - Provide education on foods containing phosphorus - Phosphorus Fact Sheet[4]
        - Recommend restricting food-based phosphate intake to 600 mg-800 mg daily[4]
    - Recommend avoiding vitamin D, phosphate-containing drugs, antacids etc.[4]
    - Refer to FGFR Inhibitor Side Effect Management PQI for additional information across the drug class

Table 1. Futibatinib Dose Adjustments Based on Phosphate Levels[1]

Drug	Serum Phosphate 5.5 mg/dL - 7 mg/dL	Serum Phosphate 7.0 mg/dL - 10.0 mg/dL	Serum Phosphate >10 mg/dL
Futibatinib (Lytgobi®) Onset: about 1 week	• Continue Futibatinib at the current dose and initiate phosphate lowering therapy • Monitor serum phosphate weekly	• Initiate or adjust phosphate lowering therapy and monitor serum phosphate weekly • Dose reduce Futibatinib to next lower dose o If the serum phosphate resolves to ≤ 7 mg/dL within 2 weeks after dose reduction, continue at this reduced dose o If serum phosphate is not ≤ 7 mg/dL within 2 weeks, further reduce to the next lower dose o If serum phosphate is not ≤ 7 mg/dL within 2 weeks after the second dose reduction, withhold until serum phosphate is ≤ 7 mg/dL and resume at the dose prior to suspending	• Initiate or adjust phosphate lowering therapy and monitor serum phosphate weekly • Withhold futibatinib until phosphate is ≤ 7 mg/dL and resume at the next lower dose • Permanently discontinue if serum phosphate is not ≤ 7 mg/dL within 2 weeks following 2 dose interruptions and reductions

Toxicity (Onset)	Recommendation[1-8]
Ocular (Within first 2 treatment cycles, resolves upon discontinuation[5])	o Recommend ophthalmologic evaluation at baseline and then every 2 months for the first 6 months, and every 3 months thereafter during treatment[1] o Ocular lubricants may be prescribed prophylactically to prevent dry eyes in all patients receiving FGFR inhibitors[3] ▪ Recommend obtaining artificial tears or lubricating eye gels over the counter and apply up to every 2 hours while awake for dry eyes o Grade 1–3 toxicity ▪ Resolved within 14 days: Continue at current dose ▪ Not resolved within 14 days: Hold until resolved, then resume at pervious or lower dose with a close follow up with ophthalmology o Grade 1 toxicity: Dose-escalation may be considered if the patient tolerated the lowered dose for at least 2 cycles[3] o Grade 4 toxicity: Permanently discontinue[3]
Stomatitis (1-2 weeks)	o Emphasize the need for proper oral hygiene o Avoidance of salty, spicy, or citrus-based foods, as well as hot beverages[3]

	○ Grade 1-2: dexamethasone 0.5 mg/5 mL elixir is recommended[6] ○ Grade 3: Hold until resolved to Grade 1 or baseline, then resume at next lower dose ○ Grade 4: Permanently discontinue ○ Recommend warm rinse of mouth with mixture of baking soda/salt ○ Recommend Magic Mouth Wash as needed
Dry Skin (1-2 weeks)	○ Moisturize skin often and thoroughly[6] ○ Avoid exposure to lotions/soaps with fragrance[6] ○ Urea containing (10-25%) preparations may help prevent transepidermal water loss[6] ○ Recommend obtaining salicylic acid preparations over the counter for their keratolytic, bacteriostatic, and fungicidal effects[6] ○ Grade 3 xerosis: Hold until resolved to Grade 1 or baseline, then resume at next lower dose; hydrocortisone 2.5% cream/ointment or triamcinolone 0.1% cream are recommended[6] ○ Grade 4: Permanently discontinue
Dry Mouth (1-2 weeks)	○ Recommend obtaining gustatory and masticatory stimulants for dry mouth over the counter such as ACT Dry Mouth Lozenges with Xylitol ○ Recommend obtaining mucosal lubricants/saliva substitutes with carboxymethylcellulose over the counter such as Biotene Mouthwash or gel

PPES
(2-4 weeks)
	○ Prophylactic removal of hyperkeratotic areas, pedicures, and cushioning of callused areas[6]
	○ Avoidance of activities that cause force/rubbing on the hands/feet during the first 6 weeks[6]
	○ Limiting contact with harsh chemicals and sources of heat[6]
	○ Recommend initiation of topical cream with urea 10-25% at start of FGFR inhibitor
	  ○ Apply Udderly Smooth Extra Care 20 (20% urea) or Flexitol Heel Balm with 25% urea three times a day to palms and soles
	○ Grade ≥ 1: urea ≥ 10% cream[6]
	○ Grade ≥ 3: Hold until resolved to Grade 1 or baseline, then resume at next lower dose; urea cream plus moderate/high potency topical corticosteroid – apply to palms and soles
	  ○ Moderate potency: generic Triamcinolone acetonide 0.1% cream/ointment or Flurandrenolide 0.005% (Cordran cream/ointment)
	  ○ High potency: Fluocinonide 0.05%
	○ Grade 4: Permanently discontinue

Nail Changes (1-2 months)	○ Trimming raised distal nail and keep nails clipped, use of topical emollients, protective gloves and loose fitting socks/footwear[6] ○ Consider dermatology consult and recommend medical attention if concerned for infection ○ Recommend clindamycin 1% solution or mupirocin ointment around and under nails three times a day for infection ○ Recommend soaking in 1:1 vinegar/tap water mix for 15 minutes daily ○ Grade 3: Hold until resolved to Grade 1 or baseline, then resume at next lower dose ○ Grade 4: Permanently discontinue

References:

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