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Positive Quality Intervention: FGFR Inhibitor Side Effect Management

Description: Fibroblast growth factor receptor (FGFR) inhibitors are a class of oral oncolytics approved for certain FGFR-altered malignancies, including bladder cancer (erdafitinib) and cholangiocarcinoma (infigratinib and pemigatinib). FGFR inhibitors come with unique adverse effect profiles and monitoring considerations. The purpose of this PQI is to provide multidisciplinary team members with key education, monitoring, and supportive care considerations for patients on these therapies.

Background: The FGFR family of proteins (FGFR 1-4) are transmembrane tyrosine kinase signaling proteins with several physiologic functions including cell proliferation, differentiation, embryogenesis, angiogenesis and phosphate homeostasis.[1] FGFR mutations and fusions can drive cancer growth via increased cell proliferation and survival, angiogenesis, and resistance to anticancer agents.[2] The first FDA-approved FGFR inhibitor, erdafitinib is a pan-FGFR inhibitor indicated for advanced or metastatic urothelial carcinoma with susceptible FGFR 2 or 3 genetic mutations and translocations after progression on at least 1 platinum-containing chemotherapy.[3] Erdafitinib demonstrated an objective response rate of 40% in the phase II BCL2001 trial.[4] Both pemigatinib and infigratinib inhibit FGFR 1-3 and are approved for previously treated, unresectable advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement. Pemigatinib demonstrated a 36% objective response rate in the FGFR2-altered population of the phase II FIGHT-202 trial.[5] Infigratinib yielded a 19% objective response rate patients with FGFR2 fusions in a phase II trial.[6] All three agents were approved under the accelerated approval pathway, with final approval pending results of phase III trials.
Due to the unique physiologic roles of FGFR kinases, FGFR inhibitors have unique toxicity profiles. Hyperphosphatemia is a key on-target adverse effect of the FGFR inhibitors and requires specific monitoring. Furthermore, hyperphosphatemia may predict superior outcomes – erdafitinib requires a dose increase for those who do not experience hyperphosphatemia to optimize its efficacy.[7] Other side effects also deserve attention including ocular toxicities, dermatologic toxicities, diarrhea, and fatigue. Each of these agents also carries the risk for fetal harm due to the role of FGFR in embryonal development.

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

- Review patient's history, including diagnosis and prior treatments
- Verify the presence of a susceptible FGFR alteration for that drug or malignancy
    - Erdafitinib: select FGFR2 fusions, FGFR3 fusions, or FGFR3 mutations
    - Pemigatinib and infigratinib: select FGFR2 fusions or other arrangements
- Assess baseline renal and hepatic function and need for any initial dose reductions (*Table 1*)
- Review concomitant medications for interactions, dose adjustments, or spacing as appropriate
- 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
- Ensure ophthalmologic exams at baseline and at appropriate intervals throughout treatment (*Table 1*)

Patient Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) sheet for appropriate FGFR inhibitor to patient

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- Review dosing schedule and calendar with patient
- Discuss signs and symptoms of hyperphosphatemia: muscle cramps, numbness, tingling in the mouth
- For patients on erdafitinib, discuss implementing a low-phosphate diet before the initial dose increase period (14-21 days) with a goal of less than 600 - 800 mg phosphate in a day[3] and should also avoid medications that increase phosphate including supplements, vitamin D, and some antacids
    - High phosphate foods: dairy, beans, lentils, processed meats, nuts, sodas with phosphates
    - Low phosphate foods: fresh fruits and vegetables, rice, fish, breads, pasta
- Discuss dry eye and symptoms of ocular toxicity (central serous retinopathy/retinal pigment epithelial detachment): blurred vision, loss of vision, or other visual changes
- Provide expectations for lab monitoring when starting therapy, especially during the first 2-3 months
- Review dosing with patients as dose reductions occur to ensure proper administration
- Medications should be stored in a cool, dry place at room temperature
- FGFR inhibitors should be taken at about the same time each day *If a dose is missed, doses should not be doubled, they should be logged, and reported to the provider
- Patient assistance
    - Erdafitinib: https://www.balversa.com/support-resources/cost-support
    - Pemigatinib: https://hcp.incytecares.com/pemazyre/home.aspx
    - Infigratinib: https://www.truseltiq.com/hcp/forging-bridges-overview

References

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9. *Truseltiq. Package Insert.* QED Therapeutics, Inc.

Supplemental Information:

Table 1. Dosing and Monitoring Guideline Summary

	Erdafitinib (Balversa®)[3]	**Pemigatinib (Pemazyre®)[8]**	**Infigratinib (Truseltiq™)[9]**
FDA Indication	Advanced or metastatic urothelial carcinoma with susceptible FGFR2 or 3 genetic mutations after at least 1 platinum-containing chemotherapy	Unresectable advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement, after previous treatment	Unresectable advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement, after previous treatment
Dosing	8 mg (2 x 4 mg tablet) PO daily Increase dose to 9 mg (3 x 3 mg tablet) daily after 14-21 days if phosphate < 5.5 mg/dL and no ocular or grade ≥ 2 toxicity. Take with or without food	13.5 mg (1 x 13.5 mg tablet) PO daily for 14 consecutive days of a 21-day cycle. Take with or without food	125 mg (1 x 100 mg plus 1 x 25 mg capsules) PO daily for 21 consecutive days of a 28-day cycle Administer on an **empty stomach** at least 1 hour before or 2 hours after food
Dosage forms	3 mg, 4 mg, 5 mg tablet	4.5 mg, 9 mg, 13.5 mg tablet	100 mg, 25 mg capsule
Dose reductions	8 mg → 6 mg → 5 mg → 4 mg → discontinue	13.5 mg → 9 mg → 4.5 mg → discontinue	125 mg → 100 mg → 75 mg → 50 mg → discontinue
Use in organ dysfunction	Renal impairment: No adjustment required Hepatic impairment: No adjustment required	Renal impairment: Dose reduction required for eGFR < 30 mL/min/1.73m^2 Hepatic impairment: Dose reduction required for bilirubin >3 times ULN	Renal impairment: Dose reduction required for CrCl 30-89 mL/min, for CrCl < 30mL/min specific recommendations are not established Hepatic impairment: Dose reduction required for bilirubin or AST above ULN
Pregnancy	Use contraception during treatment and for 1 month after last dose	Use contraception during treatment and for 1 week after last dose	Use contraception during treatment and for 1 month after last dose
Drug-Drug or Food-Drug interactions	CYP3A4 and CYP2C9 inducers and inhibitors Restrict phosphate intake to 600 to 800 mg daily during the initial dose adjustment period. Avoid vitamin D supplements, antacids, phosphate-containing enemas or laxatives, or other medications with phosphate excipients	CYP3A4 inducers and inhibitors	CYP3A4 inducers and inhibitors Avoid use with PPIs. If H2RAs must be used, administer infigratinib 2 hours before or 10 hours after. Administer infigratinib 2 hours before or after mineral antacids Take on an empty stomach due to increased absorption with food

Monitoring			
Serum phosphate	Baseline, day 14-21, then monthly Median time to onset: 20 days	As clinically necessary (monitor weekly if hyperphosphatemia develops) Median time to onset: 8 days	As clinically necessary (monitor weekly for serum phosphate >5.5 mg/dL) Median time to onset: 8 days
Eye exams, including optical coherence tomography	Baseline, monthly x 4 months, then every 3 months thereafter and as clinically necessary Median time to onset: 50 days	Baseline, every 2 months x 6 months, then every 3 months thereafter and as clinically necessary Median time to onset: 62 days	Baseline, at 1 month, at 3 months, then every 3 months thereafter and as clinically necessary Median time to onset: 26 days
Common adverse drug reactions	Fatigue, onycholysis, alopecia, paronychia, stomatitis, diarrhea/constipation, decreased appetite, dysgeusia, nausea Increased ALT, AST, alkaline phosphatase, creatinine, phosphate Decreased sodium, albumin, magnesium, hemoglobin	Alopecia, nail changes, constipation/diarrhea, dysgeusia, nausea, decreased appetite, fatigue Increased serum creatinine, ALT, AST, bilirubin, calcium, glucose Decreased albumin, sodium	Alopecia, nail changes, abnormal eyelash growth, constipation/diarrhea, decreased appetite, dysgeusia, fatigue, epistaxis Increased phosphate, triglycerides, creatinine Decreased sodium, ALT, AST, alkaline phosphatase, bilirubin

Table 2. Clinical Trial Summary

	Patient Population	**Description**	**Outcome**
BLC2001 Study	Locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 or FGFR2 alterations	Erdafitinib	Objective tumor response 40% Median duration of PFS 5.5 months Median duration of OS 13.8 months
FIGHT-202 Study	Unresectable, locally advanced, metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement	Pemigatinib	Objective tumor response 35.5% Median DOR 7.5 months (5.7-14.5 months)
CBGJ398X2204 Study	Previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement	Infigratinib	ORR 23.1% (95% CI 15.6-32.2) Median DOR 5.0 months (0.9-19.1 months)

PFS: Progression Free Survival, OS: Overall Survival, DOR: Duration of Response, ORR: Overall Response Rate