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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), cholangiocarcinoma (infigratinib and pemigatinib), and intrahepatic cholangiocarcinoma (futibatinib). 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 Oral Chemotherapy Education (OCE) sheet for appropriate FGFR inhibitor to patient
- 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: NCODA Financial Assistance Tool

References:

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3. Balversa (erdafitinib) [Package Insert].
4. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med*. 2019;381(4):338-348. doi:10.1056/NEJMoa1817323.
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6. Makawita S, K Abou-Alfa G, Roychowdhury S, et al. Infigratinib in patients with advanced cholangiocarcinoma with *FGFR2* gene fusions/translocations: the PROOF 301 trial. *Future Oncol*. 2020;16(30):2375-2384. doi:10.2217/fon-2020-0299.
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8. Pemazyre (pemigatinib) [Package Insert].
9. Truseltiq (infigratinib) [Package Insert].
10. Lytgobi (futibatinib) [Package Insert].

Supplemental Information:

Table 1. Dosing and Monitoring Guideline Summary

	Erdafitinib (Balversa®)[3]	**Pemigatinib (Pemazyre®)[8]**	**Infigratinib (Truseltiq™)[9]**	**Futibatinib (Lytgobi®)[10]**
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.	Previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 fusion or other rearrangements.
Dosing	8 mg PO daily. Increase dose to 9 mg 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 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.	20 mg PO (five 4 mg tablets) once daily. Take with or without food.
Forms	3 mg, 4 mg, 5 mg tablet	4.5 mg, 9 mg, 13.5 mg tablet	100 mg, 25 mg capsule	4 mg tablet
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	20 mg → 16 mg → 12 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.	Renal impairment: No adjustment required. Hepatic impairment: No adjustment required.
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.	Use contraception during treatment and for 1 week 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.	CYP3A4 inducers and inhibitors.
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.	As clinically necessary (monitor weekly for serum phosphate >5.5 mg/dL). Adjustment needed for serum phosphate >7 - ≤ 10. Median onset 5 days.

Eye exams	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.	Baseline, every 2 months x 6 months, then every 3 months thereafter and as clinically necessary. Median time to onset 40 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.	Nail toxicity, musculoskeletal pain, constipation, diarrhea, fatigue, dry mouth, alopecia, stomatitis, abdominal pain, dry skin, arthralgia, dysgeusia, dry eye, nausea, decreased appetite, urinary tract infection, palmar-plantar erythrodysesthesia syndrome, and vomiting. Increased phosphate, creatinine, glucose, calcium, ALT, AST, activated partial thromboplastin time, bilirubin, prothrombin. Decreased hemoglobin, sodium, phosphate, lymphocyte, platelets, leukocytes, albumin, neutrophils, increased creatine kinase, increased bilirubin, glucose, potassium.