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Positive Quality Intervention: Management of Infigratinib (Truseltiq™) in Cholangiocarcinoma

Description: This PQI will discuss the role of infigratinib in cholangiocarcinoma treatment along with prescribing specifics and adverse effects.

Background: Infigratinib belongs to the class of agents which target the fibroblast growth factor receptor 2 (FGFR2). FGFR2 fusions and rearrangements play a key role in cholangiocarcinoma.[1] Cholangiocarinomas are a heterogenous group of rare malignancies of the biliary tree and are divided based on anatomic location to intrahepatic, extrahepatic, and hilar.[2] Each encompass intricacies in presentation and management. FGFR2 fusions and rearrangements are more commonly (~15%) seen in those with intrahepatic cholangiocarcinoma which often present in the advanced incurable setting due to vague symptoms. Intrahepatic cholangiocarcinomas carry a poor prognosis. Following front-line treatment, second-line treatment lacks a standard across all advanced cholangiocarcinoma patients and traditional chemotherapy approach has proven to have minimal to no benefit (5% objective response rate and median PFS of 4 months).[3] Best practice is to molecularly profile all intrahepatic cholangiocarcinoma tumors to determine actional targetable mutations such as that seen with FGFR2 fusions and rearrangements.[2] In May 2021, infigratinib was granted accelerated FDA approval based on results of a phase 2 trial.[1] Javle et al performed a multicenter, open-label, single arm study of infigratinib 125 mg po daily for 21 days and 7 days off in previously treated advanced or metastatic cholangiocarcinoma patients with FGFR2 fusions or rearrangements.[4] One hundred and eight patients received at least one dose of infigratinib. Objective response rate was 23.1% with one complete response reported and 24 partial responses. Another 61% showed stable disease. Median PFS was 7.3 months. Grade 3 adverse events that occurred in $\geq$ 10% were hyperphosphatemia (10%), stomatitis (15%), hypophosphatemia (12%), and hyponatremia (13%). FGFR inhibitor class adverse effects include hyperphosphatemia, hypophosphatemia, nail changes, alopecia, myalgias/arthralgias, dry eye, taste changes, and rare retinal pigment epithelial detachment.[1]

PQI Process:[1]

- Confirm diagnosis for advanced cholangiocarcinoma with FGFR2 fusion or rearrangement
- Confirm progression on at least one prior line of therapy
- Verify dosing: recommended starting dose is 125 mg po daily x 21 days then 7 days off on an empty stomach (1 hour before or 2 hours after food)
    - Dose modifications for renal and hepatic dysfunction
- Check for drug-drug interactions as strong and moderate CYP3A4 inhibitors and inducers should be avoided and acid-reducing agents should be avoided
    - If unavoidable, dosing of histamine-2 antagonist or antacids should be staggered to avoid co-administration with infigratinib (2 hours before or after antacids; 2 hours before or 10 hours after histamine-2 antagonists)
- Monitoring includes ophthalmic exam at baseline, 1 month, at 3 months, and every 3 months while on therapy and phosphorus monitoring
- Dose modifications:

1st dose reduction	2nd dose reduction	3rd dose reduction
100 mg po daily for 21 days then 7 days off	75 mg po daily for 21 days then 7 days off	50 mg po daily 21 days with 7 days off

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- Dose modifications for hyperphosphatemia:

Hyperphosphatemia Severity	Dose modifications & recommendations
Serum phosphate >5.5 - ≤7.5 mg/dL	Continue infigratinib at the current dose and start/adjust a phosphate binder • Dosing for phosphate binder should be held during the week off infigratinib therapy each cycle (Days 22-28) and during any dose interruptions for infigratinib non-hyperphosphatemia adverse events
Serum phosphate >7.5 mg/dL **or** Single serum phosphate >9 mg/dL regardless of duration or dose of phosphate lowering therapy	Hold infigratinib until serum phosphate ≤ 5.5 mg/dL Resume infigratinib as below, with maximal phosphate binder dosing: • If serum phosphate >7.5 mg/dL occurred for < 7 days: Restart infigratinib at the same dose • If serum phosphate >7.5 mg/dL for >7 days or if patient had a one-time serum phosphate of >9 mg/dL: Resume infigratinib at the next lower dose level
Serum phosphate with life threatening consequences; urgent intervention indicated (ex. dialysis)	Permanently discontinue infigratinib

Patient Centered Activities:[1]

- Provide Oral Chemotherapy Education Sheet
- Instruct patient to take at the same time a day on an empty stomach for 21 days then 7 days off
- Educate patient that if a dose is missed greater than 4 hours skip the medication for that day
- Counsel patient on phosphate lowering diet and the important of following up with healthcare professional for routine lab monitoring
- Educate patient to review any new medications with healthcare team prior to starting given the potential for drug-drug interactions
- Discuss avoidance of grapefruit and grapefruit juice due to drug-food interaction
- Instruct patients to use effective contraception during treatment and for one month after final dose
- Counsel patient on signs of retinal pigment detachment and the importance of following up at specific time intervals with ophthalmologist exams

References:

1. TRUSELTIQ™ (infigratinib) [prescribing information].
2. National Comprehensive Cancer Network. Hepatobiliary Cancers.
3. Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021 may, 22(5): 690-701.
4. Javle M, Roychowdhury S, Kelley RK, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. Lancet Gastroenterol Hepatol. 2021; 6: 803-815.