Written By: Sarah Rockwell, PharmD, BCOP
Moffitt Cancer Center

Positive Quality Intervention: Pacritinib (Vonjo™) in Cytopenic Myelofibrosis

Description: The purpose of this PQI is to discuss clinical considerations and adverse effect management surrounding the use of pacritinib (Vonjo™) in myelofibrosis (MF) and thrombocytopenia.

Background: Pacritinib is an oral kinase inhibitor with activity against JAK2, mutant $JAK2^{V617F}$, IRAK1, and FLT3. Pacritinib is FDA approved for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) MF with a platelet count below 50 x 10^9/L. Pacritinib was approved based on efficacy in spleen volume reduction demonstrated in the PERSIST-2 trial. The PERSIST-2 trial was a phase 3 randomized international multi-centered study comparing pacritinib to best available therapy (BAT), which included any physician-selected treatment for MF (including ruxolitinib). In this trial, 311 patients were randomized 1:1:1 to pacritinib 400 mg once daily, pacritinib 200 mg twice daily, or BAT. The most common adverse reactions in ≥20% of patients taking pacritinib 200 mg twice daily were diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema. From this group, serious adverse reactions occurred in 47% of patients, compared to 31% of patients treated with BAT. Of these, the most frequent serious adverse reactions included anemia (8%), thrombocytopenia (6%), pneumonia (6%), cardiac failure (4%), disease progression (3%), pyrexia (3%) and squamous cell carcinoma of the skin (3%). NCCN guidelines recommend pacritinib as first-line therapy for patients with high-risk myelofibrosis, not transplant eligible, with a platelet count <50,000. NCCN also recommends pacritinib in high-risk MF patients with platelets >50,000 following one prior JAK inhibitor.

PQI Process: When prescribing or receiving a new prescription for pacritinib:

- **Review dosing and administration**: The recommended starting dose is 200 mg orally twice daily, taken with or without food (capsules should not be opened, broken, or chewed)
  - Pharmacokinetic Considerations:
    - Avoid in patients with moderate Child-Pugh B or severe Child-Pugh C hepatic impairment
    - Avoid in patients with eGFR less than 30 mL/min
  - Additional Considerations:
    - If patient is on alternative kinase inhibitor: taper/discontinue according to prescribing information prior to initiation of pacritinib
    - Control pre-existing diarrhea prior to pacritinib initiation
    - Avoid use in patients with active bleeding and baseline QTc prolongation
    - Hold pacritinib 7 days prior to any planned surgical or invasive procedures
    - Delay starting pacritinib until active/serious infections have resolved
    - Correct any electrolyte imbalances prior to initiating pacritinib
  - Missed Doses:
    - Do not make up missed doses; take the next prescribed dose at its scheduled time
- **Review drug-drug interactions:**
  - Contraindicated with strong CYP3A4 inhibitors or inducers
  - Avoid use with moderate CYP3A4 inhibitors or inducers
  - Avoid use with sensitive substrates of CYP1A2, CYP3A4, P-gp, BCRP, or OCT1
- **Lab Monitoring/Additional Testing:**
  - Obtain Complete Blood Count and coagulation testing at baseline and as clinically indicated throughout treatment
  - Obtain baseline electrocardiogram and as clinically indicated throughout treatment

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Assess adverse effects and hold therapy or modify dosage if indicated*:

Toxicity	Management	Dose Modifications
New onset of diarrhea or change in frequency/consistency of bowel movement	• Initiate anti-diarrheal medications • Encourage adequate oral hydration	• None for Grade 1 or 2
Grade 3 or 4 diarrhea	• **Hold pacritinib** until resolved to Grade 1 (< 4 stools/day over baseline) or lower/baseline • Intensify anti-diarrheal regimen • Provide fluid replacement • Concomitant antidiarrheal treatment is required for patients restarting pacritinib	• Restart at last given dose if resolved to Grade 1 • If diarrhea recurs **reduce dose** 50% (once toxicity resolved)
Clinically significant worsening thrombocytopenia lasting more than 7 days	• **Hold pacritinib** until resolved	• **Reduce dose 50%** (once resolved)
Moderate bleeding requiring intervention	• **Hold pacritinib** until resolved	• Restart at **last given dose** (once resolved) • If hemorrhage recurs **reduce dose 50%** (once resolved)
Severe bleeding requiring transfusion, invasive intervention, or hospitalization	• **Hold pacritinib** until resolved	• Reduce dose 50% (once resolved) • If hemorrhage recurs **discontinue pacritinib**
Life-threatening bleeding requiring urgent intervention	• **Discontinue pacritinib**	
QTc prolongation >500 msec or >60 msec from baseline	• **Hold pacritinib** until QTc prolongation resolved to ≤480 msec or baseline within 1 week • Correct hypokalemia prior/during administration	• Restart at last given dose if resolved within 1 week • If time to resolution > 1 week reduce dose (once resolved)

*General dose reductions:
- Initial starting dose: 200 mg twice daily
- First dose reduction: 100 mg twice daily
- Second dose reduction: 100 mg once daily
- *Discontinue pacritinib if further dose if unable to tolerate dose of 100 mg daily*

Patient Centered Activities:

- Provide Oral Chemotherapy Education (OCE) Sheet
  - Advise patient to note baseline bowel habits, potential for diarrhea/changes from baseline, and ensure access to antidiarrheals (ex. loperamide) and adequate hydration should diarrhea occur
    - Patients should be instructed to start taking loperamide at the first sign of any change in frequency or if bowel movements become softer, or if diarrhea occurs
  - Discuss signs and symptoms of bleeding with patient and advise to discuss with provider immediately or seek urgent medical care

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        - Educate to discuss with provider if any planned procedures, as pacritinib may need to be held
    - Discuss signs and symptoms of thrombosis with patient including deep venous thrombosis, pulmonary embolism, and arterial thrombosis and advise to seek urgent medical care if symptoms occur
    - Discuss risk of nausea/vomiting with patient and ensure access to as needed antiemetics and adequate hydration should nausea/vomiting occur
    - Discuss the potential for swelling of feet, ankles or legs and to discuss with provider if these symptoms occur
    - Ask patient to discuss any new medications with provider given potential for drug-drug interactions
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. VONJO™ (pacritinib) [prescribing information]. Seattle, WA: CTI BioPharma Corp.
2. Mascarenhas, J., Hoffman, R., Talpaz, M., Gerds, A. T., Stein, B., Gupta, V., Szoke, A., Drummond, M., Pristupa, A., Granston, T., Daly, R., Al-Fayoumi, S., Callahan, J. A., Singer, J. W., Gotlib, J., Jamieson, C., Harrison, C., Mesa, R., & Verstovsek, S. (2018, May 1). *Pacritinib vs best available therapy, including ruxolitinib, in patients with myelofibrosis: A randomized clinical trial*. JAMA oncology. Retrieved May 6, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5885169/.