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 10⁹/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%)¹. 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 pacritinib¹:

- 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

importance notice: NCODA has developed this Positive Quality Intervention platform. This platform is intended as an educational aid, does not provide individual medical advice, and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication. The materials contained in this platform do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA. NCODA does not ensure the accuracy of the information presented and assumes no liability relating to its accuracy. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. It is the individual’s sole responsibility to seek guidance from a qualified healthcare professional. Updated 1/8/24
Assess adverse effects and hold therapy or modify dosage if indicated

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<th>Toxicity</th>
<th>Management</th>
<th>Dose Modifications</th>
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| 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** |  
• Restart at last given dose if resolved within 1 week  
• If time to resolution > 1 week **reduce dose** (once resolved) |
| 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 [Treatment Support Kit (TSK)]
- 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  
  - Discuss with provider if any planned procedures, as pacritinib may need to be held
  - Educate on 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. VONJOTM (pacritinib) [prescribing information]. Seattle, WA: CTI BioPharma Corp.