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 wild type Janus associated kinase 2 (JAK2), mutant JAK2V617F, FMS-like tyrosine kinase 3 (FLT3), and interleukin 1 receptor associated kinase-1 (IRAK1) which contribute to signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Pacritinib is also an inhibitor of activin A receptor, type 1/activin receptor like-kinase 2 (ACVR1/ALK2). Pacritinib is FDA approved for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocytopenia) 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-1 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 recommends pacritinib in higher-risk MF patients, not transplant eligible, as first-line or second-line treatment regardless of platelet count and is the only preferred agent for patients with platelets <50,000/uL. NCCN also recommends pacritinib in the management of MF-associated anemia in patients with or without splenomegaly and/or constitutional symptoms.

**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
- **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

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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                                          | • 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 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
- Do not make up missed doses; take the next prescribed dose at its scheduled time

- Patient Assistance: NCODA Financial Assistance Tool

References:

1. VONJO® (pacritinib) [prescribing information]. Seattle, WA: CTI BioPharma Corp.