Hematologic cancer

MYELOFIBROSIS

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TRIAL SUMMARY: Promising results in myelofibrosis with the novel JAK-2 inhibitor, pacritinib


PERSIST-1 is a phase 3 trial comparing a novel JAK-2/FLT-3 inhibitor, pacritinib (PAC) 400 mg/day, to best available therapy (BAT) in patients with myelofibrosis (MF). PAC is a potent JAK-2 inhibitor with minimal inhibition of JAK-1 and minimal myelosuppression, making it an attractive therapeutic option in patients with MF. Patients were randomized 2:1 and stratified based on risk and platelet count (<100,000/µL and <50,000/µL). Eligibility criteria included MF (primary, post-polycythemia vera or post-essential thrombocythemia), intermediate- or high-risk disease, palpable spleen, and no prior therapy with a JAK-2 inhibitor. There were no exclusion criteria for baseline thrombocytopenia.

The study enrolled 327 patients, and the primary endpoint was spleen volume reduction (SVR) by ≥35% by week 24. Secondary endpoints were ≥50% reduction in total symptom score (TSS) by week 24 using the MPN Symptom Assessment Form. Baseline characteristics were similar between groups. Thrombocytopenia was common; 32% had platelet counts <100,000/µL and 15% had platelet counts <50,000/µL. BAT consisted of a variety of therapeutic strategies, the most common being supportive care and hydroxyurea.

Results: PAC led to a significant improvement in spleen size in all groups, including those with thrombocytopenia. SVR was seen in 19.1% for PAC vs 4.7% for BAT (p=0.0003) by intention to treat. The responses in patients with thrombocytopenia were particularly impressive, with SVR rates of 16.7% with PAC vs 0% with BAT (p=0.009) in those with platelets <100,000; and 22.9% vs 0% (p=0.045) in those with platelets <50,000. With regards to symptom control, TSS response rates were significantly higher in the PAC group, with response rates of 24.5% for PAC vs 6.5% for BAT (p<0.0001). Of note, this symptom response occurred early (weeks 4–8) in most patients. In red cell transfusion-dependent patients, 25.7% of PAC patients became transfusion-independent vs 0% of BAT patients (p=0.043). The most common adverse event was gastrointestinal toxicity, although the vast majority were low-grade and short-lived (grade 3 were <5%, <1%, <1% respectively).

COMMENTARY: Myelofibrosis patients can suffer from significant splenomegaly, disease-related symptoms and cytopenias. Treatment is often complicated by concomitant cytopenias. The PERSIST-1 trial demonstrates the efficacy and tolerability of a novel oral JAK2 inhibitor, pacritinib (PAC), characterized by minimal myelosuppression. It is the first phase 3 trial to allow patients with platelet counts <100,000/µL to enrol. Pacritinib led to a significant reduction in spleen size and improvement in MF-associated symptoms. This was achieved with minimal adverse events, the majority being mild-moderate gastrointestinal side effects. Currently, the only JAK2 inhibitor approved by Health Canada is ruxolitinib. Although ruxolitinib has revolutionized the management of MF, it is not indicated for patients with platelet counts <50,000/µL. Pacritinib may thus provide therapeutic benefit to this particularly fragile patient population. In addition, PAC led to transfusion independence in 25% of transfusion-dependent patients. The role of PAC in patients who have previously been treated with ruxolitinib and other JAK2 inhibitors is being investigated in the PERSIST-2 trial.

IN BRIEF

Already known
- Pacritinib is a potent inhibitor of JAK-2 with minimal myelosuppression.

What this study showed
- Patients with myelofibrosis, including those with low platelet counts, who were given pacritinib saw a significant improvement in spleen size compared to patients who received best available therapy; 25% of red cell transfusion-dependent patients on pacritinib became transfusion-independent, compared to 0% of patients receiving best available therapy.

Next steps
- Wait for results of the PERSIST-2 trial, which is looking at the role of pacritinib in patients previously treated with JAK-2 inhibitors.