case reports

Long-Term Hematologic Improvement in a Patient With Cytopenic Myelofibrosis Treated With Pacritinib

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Introduction

Cytopenic myelofibrosis (MF) is associated with poor prognosis and poses a therapeutic challenge because of limited treatment options. Co-occurrence of anemia and thrombocytopenia is common in MF, with at least two thirds of patients developing both.[1-3] Progressive anemia generally requires RBC transfusion,[4] which is associated with inferior quality of life.[5,6] Similarly, thrombocytopenia is associated with worse symptoms[3] and higher rates of leukemia and death.[7] Previously approved JAK1/2 inhibitors are of limited use in cytopenic patients because of treatment-related myelosuppression[8-10] in contrast to the recently approved JAK2-specific inhibitor pacritinib. Pacritinib has been associated with less myelosuppression and hematologic improvement,[1,11,12] possibly related to its unique kinome profile as an inhibitor of two inflammatory mediators, interleukin-1 receptor–associated kinase 1 (IRAK1), and activin receptor-like kinase 2, also known as activin A receptor type 1 (ACVR1).[13,14]

Pacritinib has been studied in multiple phase 2 and 3 MF trials, with a focus on spleen and symptom benefit rather than hematologic improvement and long-term outcomes.[11,12,15] Here, we report a case of a patient with MF and profound cytopenias who had ongoing hematologic improvement and symptom benefit over 4 years of pacritinib therapy.

Consent

The patient has provided written informed consent for the submission and publication of this clinical case report.

Case Report

This patient, now a 72-year-old woman, presented with symptomatic anemia (hemoglobin 8.9 g/dL) and thrombocytopenia (platelet count 27 × 10^9/L) in 2009 and was diagnosed with primary MF with a *JAK2*^{V617F} mutation. Medical history included well-controlled hypothyroidism and gastroesophageal reflux disease. Her MF was initially managed with supportive care, including erythropoiesis-stimulating agents, but in 2017, she experienced worsening disease with progressive anemia. The patient was unable to maintain a hemoglobin of 7 g/dL without frequent transfusion and was subsequently managed with transfusions every 2 weeks to maintain hemoglobin > 6 g/dL. As the cytopenias worsened, anemia restricted daily activities, and thrombocytopenia resulted in spontaneous, profuse bruising. Progressive, symptomatic splenomegaly and weight loss were reported. The patient declined allogeneic stem-cell transplantation because of the mortality risk. Instead, she enrolled in a clinical trial with the anti-CD123 antibody tagraxofusp, which was discontinued after 3 months because of lack of benefit. In March 2018, ruxolitinib was started at 5 mg daily (standard dose: 20 mg twice a day) but discontinued within 6 weeks because of worsening cytopenias and a gastrointestinal bleeding event.

In May 2018, the patient was enrolled in a dose-finding study[15] of the JAK2/IRAK1/ACVR1 inhibitor pacritinib. At this time, the DIPSS-Plus score showed high-risk disease with a median overall survival projected at 1.3 years.[16] In screening, there was bilateral lower extremity petechiae and massive splenomegaly palpable 25 cm below the costal margin. Laboratory tests revealed pancytopenia (WBCs 1.4 × 10^9/L, hemoglobin 7.7 g/dL, platelets 31 × 10^9/L). Bone marrow biopsy showed 50% cellularity, grade 3 fibrosis, 3% blasts, normal karyotype, and a high-risk mutational profile including pathological mutations in *JAK2 (variant allele frequency [VAF] 6.2%)*, *NRAS (VAF 26%)*, *GNAS (VAF 13%)*, and *ASXL1 (VAF 48%)*. The patient was randomly assigned to intermediate-dose pacritinib (100 mg twice a day) and continued until the study concluded in July 2019, after which pacritinib was administered under a compassionate use program with a subsequent transfer to commercially available drug after US Food and Drug Administration approval of pacritinib. When transitioning to compassionate use, her dose was briefly increased to 200 mg twice a day but was de-escalated to 100 mg twice a day because of gastrointestinal side effects.

Over a 4-year treatment course with pacritinib, the patient has experienced a marked improvement in

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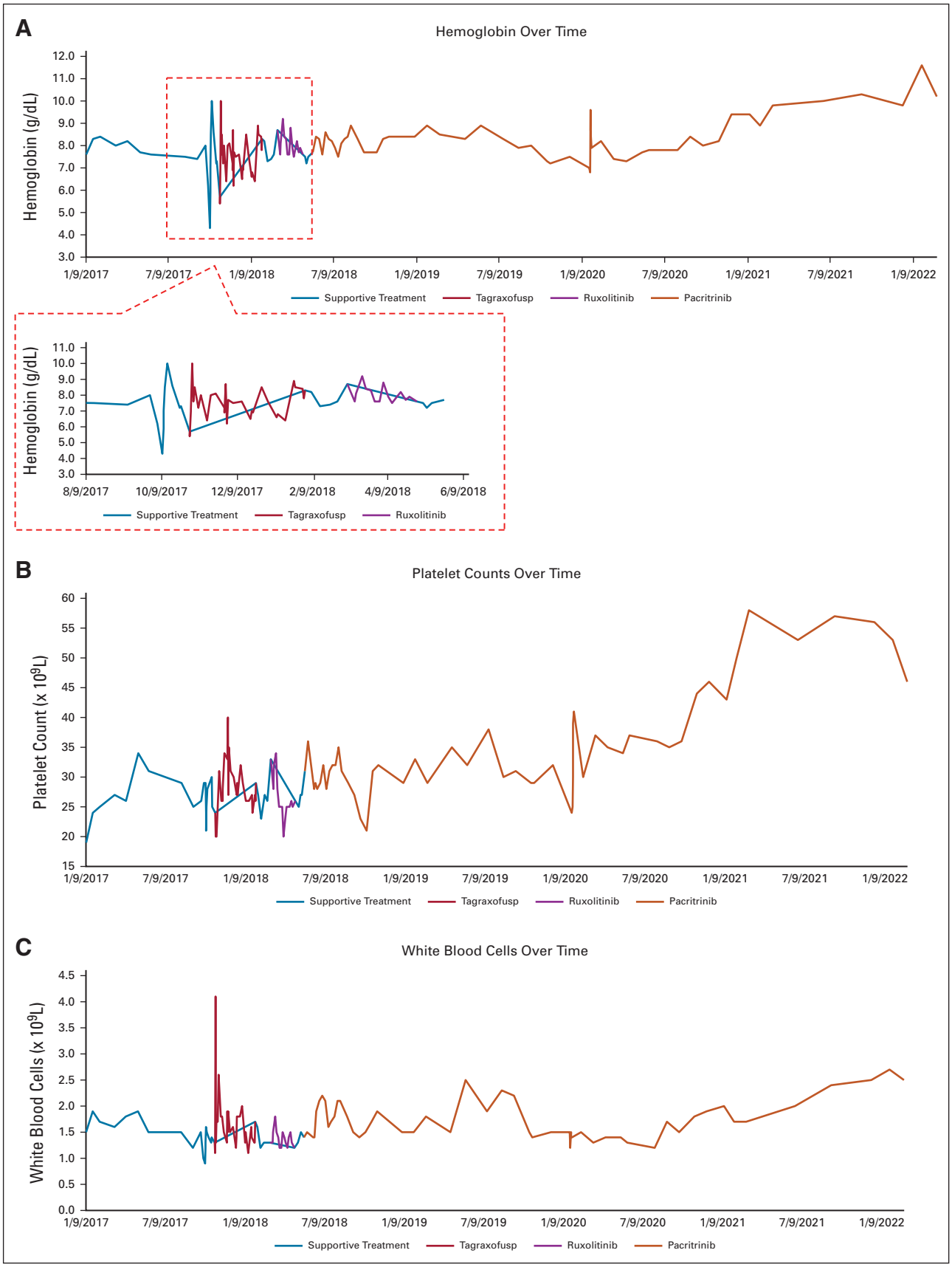

FIG 1. Blood counts over time. (A) Hemoglobin levels over time (2017-2022). (B) Platelets counts over time (2017-2022). (C) WBC over time (2017-2022).

anemia. A blood transfusion has only been required once since the start of therapy, with the hemoglobin consistently > 9 g/dL since December 2020, peaking at 11.6 g/dL (Fig 1A). The platelet count initially remained stable but rose dramatically after 2 years and has been consistently $> 50 \times 10^9$/L since that time (Fig 1B), correlating with resolution of petechiae and ecchymoses. A similar trend was observed with WBCs, which increased because of resolving neutropenia (Fig 1C). During the first 24 weeks of pacritinib therapy on study, she had 22% spleen volume reduction and reported symptom improvement. A repeat bone marrow biopsy after 4 years of therapy showed no evidence of disease progression, 80% cellularity, grade 2 fibrosis, 1% blasts, normal karyotype, and numerically stable/decreasing pathological mutations in *JAK2 (VAF 4.7%)*, *NRAS (VAF 28%)*, *GNAS (VAF 5%)*, and *ASXL1 (VAF 43%)*. Over her subsequent visits, she has reported improved appetite and decreased early satiety (including a desired 9-pound weight gain), as well as increased energy and ability to engage in daily activities and travel with family. She did not experience treatment-emergent gastrointestinal adverse events.

Discussion

This case highlights a patient with cytopenic MF who experienced dramatic improvement in all hematologic parameters while on long-term treatment with the novel JAK2 inhibitor pacritinib. Despite high clinical and molecular risk, the patient has had no evidence of pathological or molecular progression after 4 years of follow-up. The fact that these benefits occurred in conjunction with only a modest reduction in spleen volume suggests that splenic sequestration was not the major driver of this patient's cytopenias and that other features of pacritinib's inhibitory profile may have overcome the expected JAK2 class effect on anemia and thrombocytopenia. As a JAK2-selective inhibitor, pacritinib avoids the pitfalls of JAK1 inhibition on megakaryocyte maturation and platelet production.[1,17] Furthermore, it is possible that this patient's increase in hemoglobin was related to pacritinib's inhibition of ACVR1 and IRAK1.

Hepcidin is a peptide hormone that acts as a regulator of iron homeostasis and is elevated in patients with MF.[14] Pacritinib is a potent inhibitor of the key hepcidin regulator, ACVR1.[13] It has been postulated that ACVR1 inhibition reduces hepcidin, increasing iron availability for erythropoiesis.[18] Additionally, pacritinib inhibits IRAK1, a serine/threonine kinase that mediates signaling from toll-like receptors and interleukin-1.[17] Signaling from these pathways converge on NFkB, a transcription factor that regulates interleukin-6, the main cytokine implicated in stimulating hepcidin expression.[17,19]

Although this patient continues to benefit from pacritinib 100 mg twice a day, it is possible that optimal spleen response would have also been achieved had the patient tolerated 200 mg twice a day, which is the recommended starting dose for all patients regardless of baseline platelet count. This report illustrates that hematologic benefit can be attained in patients necessitating dose reduction.

In conclusion, patients with cytopenic MF are commonly intolerant of the recommended doses of JAK inhibitors because of cytopenias, leading to suboptimal response. In the case presented here, long-term pacritinib treatment improved hematologic parameters and, as a result, quality of life. These benefits may be related to pacritinib's unique mechanism of action as a JAK2/IRAK1/ACVR1 inhibitor. Ongoing work is underway by a number of groups to further delineate the role of IRAK1 and ACVR1 inhibition in MF.

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