New Advances in JAK Inhibitors and non-JAK Inhibitors in Myelofibrosis: Updates from ASH 2023

Overview

While newer-generation Janus kinase (JAK) inhibitors have improved outcomes in patients with myelofibrosis (MF), nevertheless, treatment for MF is still limited by treatment failure, dose-limiting cytopenias, and nonhematologic toxicities. At the 2023 American Society of Hematology (ASH) Annual Meeting, a series of clinical trials reported results of emerging MF therapies that have the potential to support improved outcomes in patients with MF, as each is approved. Highlights of trials include data reported from the PERSIST-2 and PAC203 trials of pacritinib, the SIMPLIFY-1 and MOMENTUM trials of momelotinib, findings of the TRANSFORM-1 trial of navitoclax, and more.

Introduction

Myelofibrosis (MF) remains a challenging myeloproliferative neoplasm to treat. For over a decade, the Janus kinase (JAK) inhibitor ruxolitinib has been the standard of care for MF. More recently, newer-generation JAK inhibitors – fedratinib, pacritinib, and momelotinib – have joined the ranks of accepted MF treatment options. However, MF treatments continue to have limitations, including treatment failure, dose-limiting cytopenias, and nonhematologic toxicities, that are attributed to high rates of treatment discontinuation.[1]

Fortunately, 2023 brought with it several important advances in MF management that are offering new hope to patients who suffer from this disease. Several of these advances were presented at the American Society of Hematology (ASH) 65th Annual Meeting and Exposition, which took place in December 2023 in San Diego, California. At this meeting, experts provided clinical trial data and insights into some of the most promising new MF treatments.

Pacritinib in PERSIST-2 and PAC203

Pacritinib is a JAK2/IRAK1/ACVR1 inhibitor that is indicated for the treatment of intermediate- or high-risk MF with platelets <50 x 10^9/L. New data have emerged from analysis of the phase 3 PERSIST-2 clinical trial, which compared pacritinib therapy to best available therapy (BAT) in cytopenic MF patients. Ajufo, et al recently found that patients treated with pacritinib in the PERSIST-2 trial who had a reduction in Total Symptom Score (TSS) ≥10% (TSS10) experienced an overall survival (OS) benefit (*P*=0.021) – an effect "*that has not been noted with other JAK inhibitors to date*," and was absent in the BAT treatment arm.[2] The study authors commented: "*It is possible that pacritinib, with its distinctive mechanism of action, may offer a unique survival advantage for MF patients with moderate or severe thrombocytopenia*."

The ability of pacritinib to be administered regardless of baseline platelet count has also caused researchers to evaluate rates of hematologic improvement in platelets (HI-P) in pacritinib-treated patients in the PERSIST-2 trial and phase 2 PAC203 study.[3] Data from these two trials showed that 19 of 117 patients (16%) in the pacritinib treatment arms experienced HI-P, 14 of whom had sustained improvement over ≥12 weeks. In contrast, just 4 of 77 individuals in the BAT arm (5%) achieved HI-P. These results did not appear to be explained by changes in spleen volume but may be the result of modulation of the bone marrow microenvironment and thrombopoiesis stemming from the mechanism of action of pacritinib as an IRAK1 inhibitor.

Momelotinib in the SIMPLIFY-1 and MOMENTUM trials

Additional research on momelotinib, a JAK1/2 inhibitor, has also been performed based on data from the phase 3 SIMPLIFY-1 and MOMENTUM trials.[4] Investigators aimed to characterize the impact of momelotinib and comparators (ruxolitinib, danazol) on transfusion burden in JAK inhibitor-naïve (SIMPLIFY-1) and -experienced (MOMENTUM) MF patients. In SIMPLIFY-1, the mean RBC transfusion burden per 28 days declined 0.10 units from baseline in the momelotinib treatment arm and increased 0.39 units in the ruxolitinib treatment arm. Additionally, 87% of those receiving momelotinib maintained or improved red blood cell (RBC) transfusion intensity during randomized treatment compared with baseline versus 54% of those receiving ruxolitinib.

In MOMENTUM, a higher proportion of patients in the momelotinib arm (35%) required zero units of RBC transfusion compared with the danazol arm (17%), while the mean RBC transfusion burden per 28 days declined 0.86 units from baseline in the momelotinib treatment arm versus 0.28 units in the danazol treatment arm. Across both trials, at least 85% of momelotinib-treated individuals maintained or improved transfusion intensity. The authors were able to conclude that momelotinib was associated with superior maintenance of RBC transfusion intensity and zero RBC transfusion status versus comparators.

Pelabresib in the MANIFEST-2 study

Pelabresib (CPI-0610) is a selective oral bromodomain and extraterminal domain (BET) inhibitor that is being investigated for MF, with preclinical data supporting the potential combination of this agent with existing therapies, such as JAK/signal transducer and activator of transcription (STAT) inhibitors. MANIFEST-2 is an ongoing phase 3 trial evaluating the combination of pelabresib and ruxolitinib versus placebo plus ruxolitinib in JAK inhibitor-naïve patients with primary MF or secondary MF (ie, post-polycythemia vera MF or post-essential thrombocytopenia MF).[5] In Arm 3 of the study, 84 patients were enrolled with a primary endpoint of spleen volume reduction (SVR) of at least 35% (SVR35) at week 24 and key secondary endpoints including 50% or more reduction in TSS (TSS50) from baseline, percentage change in TSS, and conversion from transfusion dependence to independence, among others.

At week 24, pelabresib/ruxolitinib combination therapy was found to significantly reduce splenomegaly (SVR35 66% vs 35%; $P<0.001$), double the percentage of patients with both SVR35 and TSS50 response, confer a strong trend in reducing the mean absolute TSS ($P=0.0545$) and improving TSS50 response compared with placebo. Patients in the treatment arm experienced fewer anemia adverse events (AEs) and higher rates of hemoglobin (Hb) response and were less likely to have transfusion requirement compared to those in the placebo arm. According to study author Raajit K. Rampal, MD, PhD, these findings could potentially cause a paradigm shift in the treatment of MF patients.[6]

Navitoclax in the TRANSFORM-1 study

Researchers recently evaluated the efficacy of ruxolitinib plus navitoclax, an orally available antiapoptic B-cell lymphoma 2 protein (BCL-2) inhibitor, in patients with MF. In the ongoing phase 3 double-blind, placebo-controlled TRANSFORM-1 trial, patients with JAK inhibitor-naïve MF were randomized 1:1 to receive navitoclax plus ruxolitinib or placebo plus ruxolitinib.[7] The primary endpoint was SVR35, with secondary endpoints including change in TSS, SVR35 at any time, duration of SVR35, and anemia response.

This study achieved its primary endpoint, with 63.2% of the combination treatment group achieving SVR35 at week 24 compared with 31.5% of those in the placebo treatment group. SVR35 at any time was achieved by 77% of the combination treatment group compared with 42% of the placebo treatment group (*P*<0.0001), and the median duration of SVR35 was not reached in the combination treatment arm compared with 19.4 months in the placebo arm. Combination therapy was also associated with a mean change in TSS from baseline of -9.7 (versus -11.1 among those receiving placebo, *P*=0.2852). Most AEs were considered "*manageable with dose modification without any clinically significant sequalae.*"[7]

Fedratinib in the FREEDOM2 study

Fedratinib is an oral selective inhibitor of JAK-2 and FMS-like tyrosine kinase 3 (FLT3) that was previously shown in the JAKARTA2 and FREEDOM studies to confer SVR and symptom reduction in MF patients treated with ruxolitinib.[8,9] At ASH 2023, results from the phase 3 FREEDOM2 trial comparing fedratinib to BAT in ruxolitinib-experienced MF patients were presented.[10] The primary endpoint of this study was SVR35 at end of cycle 6 (EOC6), and secondary endpoints included symptom response, SVR25, durability of SVR and symptom response, and safety.

The study authors showed that patients in the fedratinib cohort experienced significantly higher rates of SVR35 (35.8%) compared with BAT (6.0%, *P*<0.0001). Fedratinib-treated patients also had superior SVR25 and SVR35 compared with BAT, as well as higher rates of symptom response (34.1% vs. 16.9%, *P*=0.0033). In all, no new safety concerns for fedratinib were identified.

Selinexor in the XPORT-MF-034 study

Also presented at ASH 2023 were long-term results from the phase 1 XPORT-MF-034 study of selinexor and ruxolitinib therapy in JAK inhibitor-naïve MF patients.[11] Selinexor is an investigational oral XP01 inhibitor that is believed to inhibit multiple MF-relevant pathways, including STAT, ERK and AKT. This agent may also work synergistically with ruxolitinib. The XPORT-MF-034 trial enrolled 24 patients to receive selinexor 40 mg and ruxolitinib 60 mg, with assessments including safety, rate of SVR35, and TSS50, as well as platelet and Hb levels. Longitudinal clinical biomarker assessments included the percent of variant allele frequency (%VAF) change at week 24 for driver genes and plasma cytokine levels at week 4.

Of 13 patients with available data at week 24, 5 patients (38%) had a ≥20% reduction of VAF, 3 of whom had high VAF (>50%) driver mutations at baseline and were characterized as high molecular risk (HMR). This therapeutic combination also caused a rapid and durable decrease in pro-inflammatory MF-relevant cytokines (eg, TGF-β1, IFNɣ, TNF-α, IL-7, IL-1Ra, and IL-16) in the majority of the treatment group. Of interest, the reduction in IL-18 correlated to SVR and TSS response at week 24. The study authors concluded: "*Promising biomarker and efficacy data suggests that [selinexor] in combination with [ruxolitinib] has the potential to become a novel, first-line treatment for [patients] with MF*." Selinexor is intended to be evaluated in combination with ruxolitinib in JAK inhibitor-naïve MF patients in phase 3 of the XPORT-MF-034 clinical trial series, as well as alone in JAK inhibitor-naïve MF patients with moderate thrombocytopenia in the phase 2 XPORT-MF-044 study.[12,13]

In all, it is an exciting time for MF treatment, with potential shifts in standard care on the horizon. As new disease pathways and targets are discovered, it is the hope that the trajectory for patients with MF will continue to improve and that these patients will live longer, healthier lives.

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