Updates on Combination Therapies and Future Directions in Myelofibrosis

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MediCom recently spoke with two leading clinical experts to gain their perspectives on combination therapies that will have an impact on future clinical practice in myelofibrosis (MF).

Why are Janus kinase (JAK) inhibitors being combined with other therapies in MF?

Dr. Ali: JAK inhibitors have been the mainstay of treatment for MF since they were first approved in 2011. There are currently three JAK inhibitors – ruxolitinib, fedratinib, and pacritinib – that are approved for MF and a fourth, momelotinib, has a submitted New Drug Application that is currently under review by the FDA. All of these agents have been shown in large clinical trials to achieve spleen volume reduction (SVR) in a significant proportion of MF patients. These agents do differ, however, by target (JAK1, JAK2, and/or ACVR1) and indication. Ruxolitinib is currently approved for intermediate or high-risk MF. Fedratinib for similarly intermediate-2 or high-risk in the first- and second-line setting. Pacritinib is approved as a first-line therapy for patients with platelet counts less than $50x10^9$/L and as a second-line therapy for patients with high-risk intermediate MF who are progressing on the other JAK inhibitor.

The problem is that, while they are effective initially, the durability of JAK inhibitor therapy is often suboptimal and eventually, most patients progress. Therefore, we need treatment options that will be able to produce better and more durable responses. This is where combination therapy comes into play. The goal of combination therapy is to achieve faster disease control and a more durable disease response with medications with non-overlapping toxicity.

What combinations are showing promise in clinical trials?

Navitoclax

Navitoclax is a Bcl-2 inhibitor that has been combined with ruxolitinib in clinical trials in two different manners: 1) as add-on therapy when a patient has a suboptimal response to JAK inhibitor therapy, or 2) as combination front-line therapy to enhance the response to JAK inhibitor therapy. In the phase 2 REFINE trial, navitoclax was added on to ruxolitinib in patients with myelofibrosis who had progressed on or had a suboptimal response to at least 12 weeks of ruxolitinib monotherapy.[1] The study, which included 34 patients with intermediate- to high-risk MF, demonstrated a rate of SVR 35% or more (SVR35) of 26% at 24 weeks. Additionally, 30% of patients achieved a 50% or more total symptom score (TSS50) improvement, 64% experienced an improvement in hemoglobin, and about a third of patients had improvement in bone marrow fibrosis (BMF) on follow-up bone marrow biopsy. This therapy was well-tolerated, and the most common adverse event (AE) was reversible thrombocytopenia without clinically significant bleeding (88%).

The REFINE study is also evaluating ruxolitinib and navitoclax in JAK inhibitor-naïve MF patients.[2] This combination was found to achieve SVR35 in 59% to 67% of patients and BMF reduction in about a third of these patients; in fact, complete resolution of BMF was observed in 2 patients (22%). These researchers also evaluated the effect of ruxolitinib and navitoclax on JAK variant allele frequency and identified a reduction in driver gene JAK2V617 mutation VAF of more than 20% from baseline in half of the cohort, while 36% of patients achieved more than 50% VAF reduction from baseline.

In all, this data suggests that the ruxolitinib - navitoclax combination reduces splenomegaly in several high-risk groups, and the reduction in BMF and VAF for the driver mutation JAK2V617 is indicative of a potential disease-modifying effect.

This combination is now being investigated in the phase 3 TRANSFORM-1 study, which will involve patients with JAK inhibitor-naïve MF who are treated with either navitoclax plus ruxolitinib or ruxolitinib alone (NTC04472598).

Pelabresib

Another promising combination is pelabresib, a BET inhibitor, plus JAK inhibitor therapy. In the ongoing open label phase 2 MANIFEST study, pelabresib plus ruxolitinib is being evaluated in both MF patients with suboptimal ruxolitinib response (Arm 2) as well as JAK inhibitor-naïve MF

patients (Arm 3).[3] Preliminary data analysis demonstrated that, in the add-on setting, achievement of SVR35 at week 24 was 20% overall, including 17% and 26% in the transfusion-dependent (TD) and transfusion-independent (TI) patient populations, respectively. Thirty-seven percent of patients achieved TSS50, with similar proportions represented in both the TD and TI subpopulations. Alternately, in the JAK inhibitor-naïve treatment arm, SVR35 at week 24 was as high as 68% and the TSS50 was 56%. In this case, the upfront addition of pelabresib to ruxolitinib was a superior approach compared with its effect as an add-on therapy in ruxolitinib-refractory patients.

As a supplemental investigation, researchers performed an exploratory multivariable biomarker analysis on the MANIFEST data to determine if any biomarker changes corelated with SVR35, TSS50, or hemoglobin/anemia improvement.[4] They also attempted to identify any correlation between biomarkers and the JAK2V617 variant allele frequency, bone marrow morphology and/or changes in fibrosis, and plasma cytokines.

Treatment with pelabresib and ruxolitinib was found to result in BMF improvement in about 27% of the patients, while at least 20% of the study cohort had improvements in the variant allele frequency. This was shown to correlate with both hemoglobin improvement and BMF grade improvement.

Further analysis of bone marrow morphology was performed, revealing a de-clustering of megakaryocytes, wherein the distance between the megakaryocytes was increasing among patients who were on treatment at 24, 36, and 48 weeks.[5] Finally, researchers evaluated the change in inflammatory cytokines including beta-2 microglobulin, TNF receptor 2, TNF-alpha, VKM1, VGEF-alpha, and MIP-1 beta.[4] They found that patients who experienced SVR demonstrated a significant reduction in these measures.

Selinexor

An earlier-phase combination being tested is the investigational XP01 inhibitor selinexor and ruxolitinib in treatment-naïve MF.[6] Topline results of a phase 1, open-label study of this combination in 24 patients have demonstrated that treatment with selinexor and ruxolitinib produces a median decrease in hemoglobin level of 0.6 g/dL in patients with baseline hemoglobin level over 10 g/dL. Additionally, 83% and 67% of patients achieved TSS50 at weeks 12 and 24, respectively. The most common Grade 3 or higher AEs were anemia (38%), thrombocytopenia (21%), neutropenia (17%), and atrial fibrillation (13%).

What does the future of MF treatment look like?

Dr. Kuykendall: The MF community is currently keeping a close eye on INCA033989, which is a monoclonal antibody that has activity against mutant calreticulin (CALR). CALR gene mutations are strong drivers of oncogenic cell proliferation, and INCA033989 has been designed to selectively bind to mutant CALR with high affinity. Once bound, this agent inhibits CALR mutant-

dependent TPO-R dimerization and signaling transduction, which arrests subsequent oncogenic cell proliferation. This selective targeting of CALR is limited to mutated hematopoietic stem cells, preserving proliferation and differentiation of wild-type counterparts. This represents an advancement in therapy that could potentially usher in in a new era of precision medicine.

Indeed, although still in early-phase trials, this agent is showing good activity. In an evaluation of the effects of INCA033989 on CD34+ cells isolated from patients diagnosed with myeloproliferative neoplasms, INCA033989 was found to selectively inhibit phosphorylated-STAT5 in a dose-dependent manner in cells with mutant CALR, at the same time having no effect on cells harboring wild-type CALR or the JAK2V617F mutation.[7] Among the cell lineages most effected by CALR mutations, cells with mutant CALR experienced a significantly reduced rate of proliferation.

In the future, I'm optimistic that there will be additional front-line treatment options for those with thrombocytopenia, those with combination of anemia and splenomegaly symptoms, and certainly more options for patients that have anemia.

The future of second-line therapy in patients who progress in terms of splenomegaly symptoms and cytopenias is less clear, as this is an area of treatment with ongoing gaps. Patients with accelerated blast phase disease have a terrible prognosis and we need to bring more options to the table. Similarly, we really need to understand some of these non-hematologic AEs and identify if all JAK inhibitors have the same risks, or if these are specific to certain JAK inhibitors. Still, research in MF continues at a rapid pace, and I'm hopeful that the near future will be met with new, more effective treatment options.

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