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Is Doublet Therapy Becoming a Standard of Care in Myelofibrosis?

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H&O When is doublet therapy used in myelofibrosis?

RR Single-agent Janus kinase (JAK) inhibitors are the mainstay of therapy in myelofibrosis, and a total of 4 JAK inhibitors have received US Food and Drug Administration approval. Sometimes doublet regimens are used if monotherapy is ineffective, or even as first-line treatment, but these uses are off label.

H&O What doublet regimens have been used or studied?

RR Doublet therapy may combine a JAK inhibitor with an older agent, such as lenalidomide or thalidomide (Thalomid, Celgene), each of which is an immunomodulatory imide drug, or with the synthetic steroid derivative danazol. Studies have looked at all these agents in combination with ruxolitinib (Jakafi, Incyte) to see if they might reduce anemia or improve the response to treatment. We have also seen more recent data on ruxolitinib in combination with the agents navitoclax and pelabresib. Ongoing phase 3 trials are currently testing combinations of JAK inhibitors with the MDM2 inhibitor navtemadlin, the XPO1 inhibitor selinexor (Xpovio, Karyopharm), and the oligonucleotide telomerase inhibitor imetelstat (Ryelto, Geron), among others. Multiple drugs are in trials.

H&O Could you describe the research that has been done so far on navitoclax plus ruxolitinib?

RR The phase 3 TRANSFORM-1 trial, which was presented at the 2023 American Society of Hematology Annual Meeting, compared navitoclax plus ruxolitinib vs ruxolitinib alone in 252 JAK inhibitor–naive patients with myelofibrosis.[1] The primary endpoint was spleen volume reduction of at least 35% (SVR35) at 24 weeks, which was clearly superior with the combination and was achieved by 63.2% of patients in the combination group vs 31.5% of patients in the ruxolitinib group (P<.001). Furthermore, SVR35 at any time was achieved by 77% of patients in the combination group and 42% of patients in the ruxolitinib group. On the other hand, the mean change in the total symptom score at week 24 was essentially equivalent in the 2 arms, at –9.7 vs –11.1. So the combination clearly showed biological activity, but the outcome did not reach the threshold required for regulatory approval.

> We do have a lot of biological rationale for doublet therapy, which is what has led to the current clinical trials.

The addition of navitoclax to ruxolitinib also increased the rate of thrombocytopenia from 50% to 90% and the risk of grade 3 or higher thrombocytopenia from 15% to 51%. That is why we need to be cautious about combination therapies—we do not want to impose additional toxicity without a clinically significant benefit.

We also need to see longer-term data on all the drugs that are in development to really understand the risk/benefit analysis.

H&O What other studies of doublet therapy are ongoing?

RR We are still reading out data from our phase 3 MANIFEST-2 study, which is continuing to treat participants actively.[2] In this study, 430 JAK inhibitor–naive patients with myelofibrosis were randomly assigned to combination therapy with pelabresib plus ruxolitinib or to ruxolitinib alone. The primary endpoint of SVR35 at week 24 was met by 65.9% of patients in the combination arm vs 35.2% of those in the ruxolitinib-alone arm, a statistically significant difference. The absolute change in the total symptom score was –15.99 in the combination group vs –14.05 in the ruxolitinib-alone group, which was not a statistically significant difference. A trend was observed toward a higher likelihood of a reduction in the total symptom score of 50% or greater at week 24 in the combination group; the percentage of patients with this reduction was 52.3% in the combination group vs 46.3% in the ruxolitinib-alone group.

In the most recent update, which was presented at the European Hematology Association 2025 Congress, SVR35 at week 72 was achieved by 46.3% of participants in the combination arm vs 29.2% of participants in the ruxolitinib-alone arm, a statistically significant difference. Finally, grade 3 or higher treatment-emergent adverse events occurred in 65.1% and 65.4% of the participants, respectively. Grade 3 or higher anemia was more common in the ruxolitinib-alone arm, at 27.4% vs 40.7%, whereas grade 3 or higher thrombocytopenia was more prevalent in the combination arm (12.7% vs 6.1%).[3]

The phase 3 POIESIS trial is evaluating the safety and efficacy of navtemadlin plus ruxolitinib vs that of ruxolitinib alone in approximately 600 JAK inhibitor–naive patients with myelofibrosis that has not responded adequately to ruxolitinib (NCT06479135). This study is currently enrolling patients. The earlier BOREAS trial, which was presented at the 2024 American Society of Hematology Annual Meeting, showed encouraging results with navtemadlin vs best available therapy in 183 patients who had primary or secondary myelofibrosis that was relapsed or refractory to JAK inhibition.[4] At week 24, 15% of the patients assigned to navtemadlin and 5% of those assigned to best available therapy achieved the primary endpoint of the study of SVR35 at 24 weeks (P=.08). The percentage of patients with a total symptom score reduction of at least 50%, a secondary endpoint, was doubled in those assigned to navtemadlin (24% vs 12%; P=.05).

The phase 3 SENTRY trial, which is recruiting patients, is randomly assigning patients with JAK inhibitor–naive MF to selinexor plus ruxolitinib or to ruxolitinib alone (NCT04562389).

This is not a doublet regimen, but the phase 3 IMpactMF study is comparing imetelstat vs best available therapy in patients with intermediate-2 or high-risk myelofibrosis that has not responded to JAK inhibition (NCT04576156).

H&O Do you see doublet therapy becoming a standard of care in myelofibrosis?

RR At the moment, we have no approved doublet regimens. If we should see approvals, that would change the standard of care. At the end of the day, we need to wait for the data.

We do have a lot of biological rationale for doublet therapy, which is what has led to the current clinical trials. As with combination therapy for other diseases, we hope that doublets can produce a greater depth and durability of response in patients with myelofibrosis than what we have seen traditionally with single-agent JAK inhibitor therapy. We have clear evidence that doublets can have a greater clinical effect than single-agent JAK inhibitors, as has been shown in TRANSFORM-1 and MANIFEST-2. Now the question is, does this also apply to doublets with drugs that are currently in development? In addition, what will be the ultimate benefit to the patients—will they experience less disease progression or improved blood cell counts? Of course, these benefits always need to be viewed in the context of toxicities—we want to see doublets that lead to greater clinical benefit without worsening toxicity.

We also need to see longer-term data on all the drugs that are in development to really understand the risk/benefit analysis. A lot of the studies read out at 6

months. This timeline is based on the way the initial JAK inhibitor studies were done, but I am not sure that it is the best way to look at things. The newer drugs may take longer to produce an effect, and we want to see what the long-term effects are. At the end of the day, that is what is important—not just making things better in the short term without any sense of a durable effect. I would like to see these studies last for at least 2 years. This approach will make the studies more expensive to conduct, but it is the best way to address our questions about these drugs. Answering the question of whether doublets are worthwhile has proved to be a longer road than anybody anticipated.

Disclosures

Dr Rampal has been a consultant for AbbVie, Blueprint Medicines, Bristol Myers Squibb, Constellation Pharmaceuticals/MorphoSys, CTI BioPharma/Sobi, Disc Medicine, Galecto, Incyte, Jazz Pharmaceuticals, Novartis, PharmaEssentia, Promedior, Sierra Oncology/GSK, Kartos Therapeutics, Karyopharm Therapeutics, Stemline Therapeutics, Zentalis Pharmaceuticals, Sumitomo Pharma, Cogent Biosciences, and Opna Bio and has received research funding from Constellation Pharmaceuticals/MorphoSys, Incyte, Stemline, Zentalis, Ryvu Therapeutics, and Biomed Valley Discoveries.

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