Developmental Therapeutics in Myeloproliferative Neoplasms

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Abstract

The unprecedented success of the Janus kinase (JAK) 1/2 inhibitor ruxolitinib in myelofibrosis (MF) provided much-needed impetus for clinical drug development for the Philadelphia chromosome–negative myeloproliferative neoplasms. The survival benefit conferred by this agent, along with its marked efficacy with regard to spleen volume and symptom reduction, have made ruxolitinib the cornerstone of drug therapy in MF. However, there remain significant unmet needs in the treatment of patients with MF, and many novel classes of agents continue to be investigated in efforts to build on the progress made with ruxolitinib. These include inhibitors of histone deacetylases (HDACs) and DNA methyltransferases, phosphatidylinositol-3-kinase isoforms, heat shock protein 90, cyclin-dependent kinases 4/6, and Hedgehog signaling, among others. In parallel, other JAK inhibitors with potential for less myelosuppression or even improvement of anemia, greater selectivity for JAK1 or JAK2, and the ability to overcome JAK inhibitor persistence are in various stages of development. First-in-class agents such as the activin receptor IIA ligand trap sotatercept (for anemia of MF), the telomerase inhibitor imetelstat, and the antifibrotic agent PRM-151 (recombinant human pentraxin-2) are also in clinical trials. In polycythemia vera, a novel interferon administered every 2 weeks is being developed for front-line therapy in high-risk individuals, and inhibitors of human double minute 2 (HDM2) have shown promise in preclinical studies, as have HDAC inhibitors such as givinostat (both in the laboratory and in the clinic). Ruxolitinib is approved for second-line therapy of polycythemia vera and is being developed for essential thrombocythemia.

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Introduction

The marked improvement in symptoms and reduction in splenomegaly among patients with intermediate-2 or high-risk myelofibrosis (MF) receiving ruxolitinib observed in the pivotal COMFORT I and II trials compared to placebo and best available therapy (BAT), respectively, led to the approval of this agent by the US Food and Drug Administration (FDA) in 2011 for the treatment of patients with intermediate- or high-risk MF.[1,2] Additionally, an overall survival benefit of ruxolitinib treatment was observed in COMFORT I after a median follow-up of 12 months[1]; in COMFORT II, this took a median of 3 years to emerge.[3] In both trials, extensive crossover occurred after the primary end point had been assessed; despite this, the survival advantage for patients originally randomized to ruxolitinib persisted after a median of 5 years of follow-up (median survival not reached vs. 4.1 years for BAT in COMFORT II).[4] The prolongation of survival with ruxolitinib in higher-risk patients with MF has also been seen in multiple retrospective comparisons[5,6] as well as in a pooled analysis of the COMFORT trials.[7] Ruxolitinib's efficacy appears unaffected by mutational status,[8] although the number of mutations does seem to matter (lower rates of spleen response, shorter time to treatment discontinuation, and shorter overall survival in patients with $\geq$ 3 myeloid malignancy-associated mutations).[9] Spleen responses to ruxolitinib are dose dependent and correlate with survival.[5,10] While the COMFORT trials specifically studied intermediate-2 and high-risk patients, substantial data exist to support the efficacy of ruxolitinib in intermediate-1 risk patients as well.[11,12] The benefits of ruxolitinib observed in clinical trials have been recapitulated in real-life settings, including those of early initiation of treatment.[10] Accordingly, ruxolitinib is now being studied in high-molecular-risk patients without significant symptoms or splenomegaly in the placebo-controlled ReTHINK trial in Europe.[13] For the above reasons, ruxolitinib has evolved to become the standard of care for most patients with MF.[14]

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Despite these positives, ruxolitinib has several shortcomings. On-target anemia and thrombocytopenia stemming from Janus kinase (JAK) 2 inhibition are common, and the drug is difficult to use in MF patients with severe thrombocytopenia (platelets < 50,000/μL), who have a poor prognosis.[15] Furthermore, regression of bone marrow (BM) fibrosis is infrequent, and complete molecular remissions are rare.[4,16,17] As such, efforts are ongoing to develop other JAK inhibitors that are less myelosuppressive, drugs that may offset ruxolitinib-induced anemia, enabling dose optimization, find synergistic ruxolitinib-based combinations to achieve a greater disease-modifying effect in MF, and identify new therapeutic targets and novel drug classes.

Reduction of thrombotic risk is the major goal of therapy in patients with polycythemia vera (PV) and essential thrombocythemia (ET), and hydroxyurea (HU) is usually the first-line agent of choice for patients who require cytoreduction.[18] In addition, most patients should receive aspirin. In PV, achievement of hematocrit < 45% is an important goal,[19] and ruxolitinib is approved as second-line therapy for patients who are resistant or intolerant to HU[20] based on the findings of the RESPONSE trial.[21] Anagrelide is typically chosen as second-line therapy in ET.[18] Interferon preparations, while clearly active in PV and ET with the added ability to induce clonal remissions,[22-24] are not yet approved for these indications. Because of their lack of leukemogenicity, interferons are often preferred for younger, high-risk patients with PV or ET.[18]

Developmental Therapeutics in PV and ET

Interferons

As alluded to above, interferons are highly active in PV and ET. Results after a median of 7 years (82.5 months) of follow-up of a phase 2 study of pegylated interferon alfa (IFN-α)-2a conducted at the MD Anderson Cancer Center were recently presented.[25] Patients (43 PV, 40 ET) could be newly diagnosed or previously treated. The overall median exposure to therapy was 87 months. At the time of writing, 32 patients (39%) were still on the study protocol, with 9 (28%) receiving ≥ 90 μg weekly, 15 (47%) ≤ 45 μg weekly, and 8 (25%) with treatment on hold due to toxicity or financial constraints. *JAK2* status or allele burden had no impact on response (clinical or molecular), time to response, or duration of therapy. Median durations of hematologic and molecular responses were 66 and 53 months, respectively; complete molecular responses were the most durable. A total of 35% of patients discontinued therapy because of toxicity, and new, late (≥ 2 years from therapy initiation) treatment-emergent grade 3/4 toxicity was seen in 17%. Even among patients in complete hematologic remission (CHR), vascular adverse events (AEs) and disease transformation occurred in 5 patients each.[25]

The Myeloproliferative Disorders Research Consortium (MPD-RC) recently reported the results from an interim analysis (n = 75) of a global phase 3 trial of front-line pegylated IFN-α-2a compared with HU in high-risk patients with PV or ET.[26] The overall response rate (ORR) was not significantly different between the 2 arms: 69% for HU and 53% for pegylated IFN-α-2a ($P = .6$). The percentages of patients with CHR (the primary end point) in the 2 arms were similar even when the analysis was broken down by diagnosis, and also when patients who never initiated treatment were excluded. The rate of phlebotomy use among the 38 patients with PV significantly favored pegylated IFN-α-2a, which was also clearly associated with higher rates of grade 3 toxicity.[26]

Ropeginterferon alfa-2b is a next-generation monopegylated IFN-α-2b isoform with a longer elimination half-life, permitting administration every 2 weeks.[27] In a phase 1/2 study in 51 patients with PV, there were no dose-limiting toxicities, and the ORR was 90% (CHR in 47% and partial hematologic remission in 43%). The best molecular response was complete in 21% and partial in 47%. Responses did not correlate with dose.[27] On the basis of these findings, the PROUD-PV trial, a phase 3 randomized controlled trial (RCT) comparing this agent to HU in 257 patients with PV, was conducted.[28] Patients could be naive to cytoreduction or have previously received HU (cumulative exposure ≤ 3 years), but if the latter, they must not have been intolerant of HU or experienced complete response to it. This was a noninferiority trial with CHR as the primary end point. At 12 months, the rate of CHR in the ropeginterferon alfa group was 43.1% and in the HU group was 45.6%, demonstrating noninferiority ($P = .0028$). When considering CHR with normalization of spleen length, the rates were 21.3% and 27.6%, respectively, but the median spleen length at baseline was near normal, and the observed change was not clinically relevant. Cytopenias were significantly more frequent with HU, as was nausea, while increased gamma glutamyl transferase was seen significantly more frequently in the ropeginterferon alfa arm. While not statistically significant, autoimmune, endocrine, psychiatric, and cardiovascular disorders were more common among patients receiving ropeginterferon alfa.[28]

Ruxolitinib

As noted above, ruxolitinib was approved in 2014 for HU-resistant/intolerant patients with PV on the basis of the results of the RESPONSE trial.[21] In this RCT, ruxolitinib proved statistically significantly superior to BAT in terms of the primary end point, which was a composite of hematocrit control through week 32 and a ≥ 35% spleen volume reduction (SVR), as well as each individual component of the primary end point, CHR rates, and the rate of ≥ 50% reduction in the myeloproliferative neoplasm (MPN) symptom assessment form (SAF) total symptom score (TSS) at week 32.[21] Of note, the majority of patients in the BAT arm received HU despite having previously shown evidence of resistance or intolerance to this agent, reflecting the lack of effective options for this population. The benefits of ruxolitinib were sustained after a minimum of 80 weeks of follow-up.[29] Most BAT patients crossed over to ruxolitinib at or soon after week 32. Among these patients, 79.2% did not require phlebotomy, and 18.8% experienced a ≥ 35% SVR after 32 weeks of treatment. Importantly, the rate of thromboembolic events was 1.8 per 100 patient-years among patients originally randomized to ruxolitinib versus 8.2 per 100 patient-years among patients originally randomized to BAT.[29] The mean percent change from baseline *JAK2* V617F allele burden among the 104 patients randomized to ruxolitinib was −40% at week 208.[30]

Because the pivotal RESPONSE trial required the presence of splenomegaly, a finding present in less than half of PV patients at diagnosis,[31] the very similarly designed phase 3B RESPONSE-2 RCT was subsequently conducted to assess the efficacy of