JAK inhibitors: beyond spleen and symptoms?

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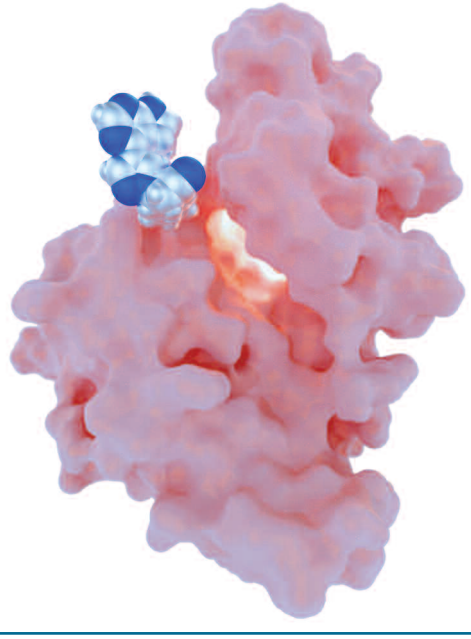
The discovery of the *JAK2V617F* mutation and constitutive JAK activation in myeloproliferative neoplasms (MPN) has radically changed the landscape of these disorders, not only triggering new diagnostic criteria but, more importantly, offering new therapeutic avenues. In 2012, results with ruxolitinib, a JAK1/JAK2 inhibitor, were reported from two randomized phase III studies comparing ruxolitinib with either placebo (COMFORT-I[1]) or best available therapy (BAT; COMFORT-II[2]) in patients with myelofibrosis (MF). The approval of ruxolitinib by the US Food and Drug Administration (FDA) in late 2011 was followed by approval in Canada and Europe, based upon efficacy in reduction of both spleen size and MF-related symptoms, as well an overall improvement in quality of life. While many, including the authors, accept these benefits to be unprecedented for patients with this difficult disorder, there has been some controversy regarding long-term safety, events upon drug withdrawal, and whether ruxolitinib treatment could prolong survival. Although a survival advantage with use of ruxolitinib has been shown in COMFORT-I compared with placebo,[1] comparing data with matched historical control groups gave conflicting results.[3,4] At the recent 2012 ASH meeting, up-dated results from both COMFORT studies were presented, broadening the data on durability of response and safety, and adding new information about survival.[5,6] Other JAK inhibitors also appear to reduce spleen size and MF-related symptoms and might offer additional benefits to ruxolitinib. Thus, phase II trial data were reported for both SAR302503[7] and CYT387.[8] In addition, novel therapies such as telomerase inhibitors were discussed.[9]

Ruxolitinib

Cervantes *et al.*[5] presented 2-year data from the COMFORT-II study. At the time of analysis, the median follow up was 112 weeks (ruxolitinib 113 weeks; BAT 108 weeks), and the median duration of exposure was 83.3 weeks (ruxolitinib 111.4 weeks; BAT 45.1 weeks). Overall, 73.3% of patients (107 of 146) in the ruxolitinib arm entered the extension phase, and 55.5% (81 of 146) of those originally randomized to ruxolitinib remained on treatment at time of the analysis. Among patients randomized to the BAT arm, 61.6% (45 of 73) crossed over to receive ruxolitinib, and the majority of them were still receiving ruxolitinib, confirming that the drug is well tolerated. These results are consistent with the long-term follow-up analysis of COMFORT-I (presented by Verstovsek *et al.*[6]) in which 100 of the 155 patients randomized to the ruxolitinib arm (64.5%) remained on treatment after a median follow up of 102 weeks.

In both studies, spleen volume reductions of 35% and over were sustained with continued ruxolitinib therapy. In COMFORT-I, mean spleen volume reduction in patients randomized to ruxolitinib was 31.6% at week 24 and has remained stable with additional follow up through week 96. In those patients who achieved a reduction in spleen volume of 35% or over, median response duration was 108 weeks. The probabilities of maintaining the spleen response on COMFORT-II for at least 48 and 84 weeks are 75% (95% CI: 61%-84%) and 58% (95% CI: 35%-76%), respectively, and the median duration of response has not yet been reached. Concerning patient-reported outcomes, long-term follow up of COMFORT-I demonstrates that ruxolitinib treatment was associated with durable clinically significant improvements in the Global Health Status/quality of life and the 5 functional domains of the EORTC QLQ-C30.[6]

No new adverse events were reported with more than two years of ruxolitinib treatment. Anemia and thrombocytopenia are anticipated and not infrequent with ruxolitinib; data indicated a lower incidence of both after week 48 (anemia 22.6%; thrombocytopenia 25.2%) and the majority were grade 1/2. In addition, as demonstrated at the time of the primary analysis for each of the COMFORT studies, anemia and thrombocytopenia rarely led to treatment discontinuation (<1% of patients in any treatment group) and were manageable with dose modifications and/or transfusions. Indeed, in the COMFORT-I study update, the proportion of patients receiving red blood cell transfusions in the ruxolitinib arm decreased to the level seen among patients receiving placebo by week 36 and remained stable thereafter.[6] Interestingly, there were no new reports of leukemic transformation in either study, and no specific pattern of adverse events or



Structure of the JAK2 kinase domain with an inhibitor going to the ATP-binding pocket.

reports of a withdrawal syndrome after discontinuation of ruxolitinib were observed with longer follow up.

As far as survival is concerned, COMFORT-I investigators continue to report that, despite the majority of patients switching to ruxolitinib from placebo, earlier treatment with ruxolitinib is associated with a survival advantage.[6] Since the last report of COMFORT-II (median 61.1 weeks),[2] an additional 9 and 12 deaths have been reported in the ruxolitinib and BAT arms, respectively, resulting in a total of 14% (20 of 146) and 22% (16 of 73) of patients overall; the median survival time has not yet been reached for either arm. For the first time in COMFORT-II, patients randomized to ruxolitinib showed longer overall survival than those randomized to BAT (HR=0.51; 95% CI: 0.27-0.99; log rank test P=0.041).[5] In COMFORT-II, the ruxolitinib and BAT arms may not have separated early in the Kaplan-Meier curve because a considerable number of patients in the BAT arm were censored prior to 48 weeks (27.4% of patients in the BAT arm *vs.* 14.4% of patients in the ruxolitinib arm). This means that they were considered alive in the absence of any further information. This factor, along with the 2:1 randomization, may bias the data in favor of BAT. However, despite these factors and the crossover of a majority of BAT patients to ruxolitinib, there was an apparent survival benefit favoring ruxolitinib in this intent-to-treat analysis. The overall survival advantage for ruxolitinib-treated patients despite the limitations described above would suggest that even the relatively short period of additional treatment for the patients initially randomized to ruxolitinib (6 months in COMFORT-I and 1 year in COMFORT-II) may have had a significant effect on survival.

These data will be followed by further updates of these studies next year. At the 2012 ASH meeting, we also heard that allele burden reductions with ruxolitinib in COMFORT-II are relatively modest.[10] Long-term data concerning marrow histology and other data, such as acquisition of new mutations, are awaited.

SAR302503

Talpaz and colleagues reported further data evaluating the JAK2 inhibitor SAR403503, presenting the results of 31 MF patients randomized in a phase II study to doses of 300, 400 and 500 mg per day.[7] All patients had completed week 12 at the time of analysis. The median percentage reduction in spleen volume from baseline ranged from 30.1% to 41.8%, with a dose-dependent increase; overall, 63.6% of patients receiving 500 mg achieved a reduction of 35% or over. There appeared to be a correlation between pharmacokinetic data and spleen response. Reduction of MF-related symptoms appears similar to other JAK2 inhibitor trial outcomes. As far as safety is concerned, the most common non-hematologic adverse events were gastrointestinal and did not lead to permanent drug discontinuation; anemia occurred but grade 3 /4 thrombocytopenia was infrequent. This agent has previously been reported to be associated with reductions in allele burden and grade of bone marrow fibrosis.[11]

CYT387

Pardanani *et al.* presented data on CYT387, a small molecule inhibitor of JAK1 and JAK2, in which preliminary results from a phase I/II multicenter study demonstrated improvements in splenomegaly and constitutional symptoms as well as in transfusion requirements.[8] A sizable cohort of 166 subjects were enrolled and the median duration of follow up was 16.1 months (range 0.7-31.0 months). Up-dated safety and efficacy results were presented when patients had reached a minimum of nine months on study. Particular novel data of interest with this compound are responses of transfusion independence which were observed in more than half of the red blood cell (RBC) transfusion-dependent subjects, with a maximal transfusion-free period exceeding two years and ongoing. In addition, over the treatment period, there was a substantial decrease in the percentage of all subjects requiring RBC transfusions. As previously reported, treatment with CYT387 resulted in rapid and sustained reductions in splenomegaly, now with a maximal response duration approaching two years; symptom responses were also encouraging yet the methodology used in this trial does make symptomatic response difficult to compare to other trial reports. Concerning safety, the most common treatment-related adverse events were thrombocytopenia, peripheral neuropathy, dizziness, diarrhea, nausea, and headache. Treatment-related peripheral neuropathy with this agent was reported as sensorial and mainly grade 1. There were no treatment-related deaths.

Conclusions

These data suggest that JAK inhibitors impact MF beyond disease-related symptomatic improvements and spleen size reduction and offer major benefits to patients. During this year, data from year 3 of the COMFORT studies are expected, as well as the results of the JAKARTA phase III study with SAR302503 and from the RESUME, a phase III placebo controlled study with pomalidomide (a new immunomodulator agent) in MF patients with transfusion-dependent anemia. Intriguing and important data from the first studies of JAK inhibitors in combination with other agents should mature and results from JAKARTA-2, a study of SAR302503 in patients refractory or intolerant to ruxolitinib, may be reported. The activity of these agents in low- and intermediate-1 risk MF patients (who can have splenomegaly- or significant MF-related symptom burden[12]) merits careful study. Lastly, the advent of JAK inhibitor therapy and new data from clinical studies suggest the need for better and more meaningful definitions of response and disease progression.

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