Ruxolitinib treatment for myelofibrosis

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Ruxolitinib, a JAK 1/JAK 2 kinase inhibitor, was recently approved by the Food and Drug Administration for the treatment of patients with intermediate- or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocythemia myelofibrosis. JAK kinases mediate signaling of cytokines and growth factors that are involved in hematopoiesis and immune function. JAK signaling involves the recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, STAT activation, and localization of STATs to the nucleus, which results in the modulation of gene expression. Myelofibrosis is associated with aberrant JAK signaling. Ruxolitinib acts to attenuate downstream signaling by inhibiting JAK 1 and JAK 2 kinases, which results in reduced plasma cytokine levels and the induction of antiproliferative and proapoptotic effects (Figure).

Ruxolitinib was evaluated in 2 phase 3 trials in patients with intermediate- or high-risk myelofibrosis: a double-blind trial that compared ruxolitinib (155 patients, 15-20 mg orally twice daily based on baseline platelet counts) with placebo (154 patients) and an open-label trial that compared ruxolitinib (146 patients, same dosage) with the best available therapy (73 patients).[1] Ruxolitinib treatment was continued for as long as patients benefited from the therapy or until they experienced unacceptable therapy-related toxicity. The primary study end points were the proportions of patients with a 35% or greater reduction in spleen volume at 24 weeks in the double-blind trial and at 48 weeks in the open-label trial.

In the double-blind trial, patients had a median age of 68 years (with 61% older than 65 years), and 54% were men. In all, 50% of the patients had primary myelofibrosis, 31% had post-polycythemia vera myelofibrosis, and 18% had post-essential thrombocythemia myelofibrosis; 21% had received red blood cell (RBC) transfusions within 8 weeks of study enrollment in the study. The median hemoglobin count was 10.5 g/dL and the median platelet count was 251 x 10^9/L. The patients had a median palpable spleen length of 16 cm below the costal margin, with 81% having a spleen length of 10 cm or more below the costal margin. The median spleen volume as measured by magnetic resonance imaging (MRI) or computed tomography (CT) was 2,595 cm^3 (range, 478-8,881 cm^3).

What's new, what's important

Myeloproliferative disorders are clonal disorders characterized by increased production of mature cells. In most of the classic Philadelphia-negative polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF)-oncogenic mutations affecting JAK2 or MPL lead to constitutive activation of cytokine-regulated intracellular signaling pathways. Myelofibrosis (MF), either primary or arising from previous PV or ET has the worst prognosis among the chronic myeloproliferative neoplasms as far as survival and quality of life are concerned.

The risk-stratification systems, at diagnosis using the International Prognostic Scoring System (IPSS) or during the course of illness using the Dynamic International Prognostic Scoring System (DIPSS) and DIPSS Plus, allow the clinicians to categorize patients based on survival durations ranging from decades to less than 2 years. The discovery of the JAK2V617F mutation is an important milestone in diagnosis and treatment of MF.

At the end of last year, the Food and Drug Administration approved for the treatment of intermediate and high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis and postessential thrombocythemia myelofibrosis. The recommended starting dose of ruxolitinib is 20 mg orally twice daily for patients with a platelet count > 200 x 10^9/L and 15 mg orally twice daily for patients with a platelet count between 100 x 10^9/L and 200 x 10^9/L. The most common adverse drug reactions observed in 1% or fewer of the patients treated with ruxolitinib included thrombocytopenia, anemia, bruising, dizziness, and headache.

Ruxolitinib has resulted in meaningful symptomatic improvement and reduction of splenomegaly that were otherwise not achievable with conventional therapy. This is an important development for patients with this aggressive refractory diagnosis.

— Jame Abraham, MD

In the open-label trial, patients had a median age of 66 years (with 52% older than 65 years), and 57% were men.

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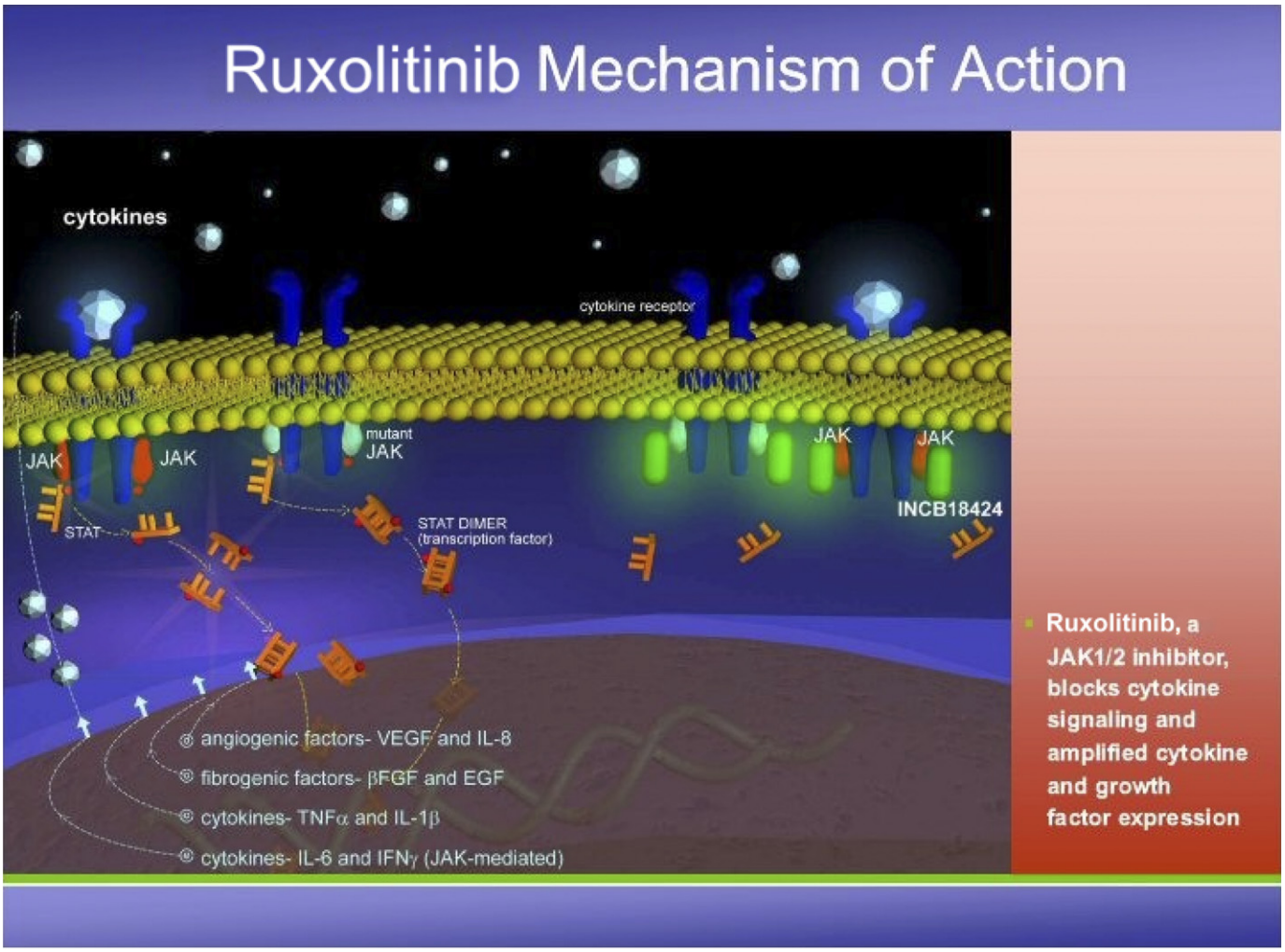

FIGURE Ruxolitinib is a JAK 1 and JAK 2 kinase inhibitor that acts to block downstream signaling, inhibiting cytokine and growth factor expression and resulting in reduced plasma cytokine levels and antiproliferative and proapoptotic effects. Figure from http://www.incyte.com/drugs_product_pipeline.html.

In all, 53% of patients had primary myelofibrosis, 31% had post-polycythemia vera myelofibrosis, and 16% had post-essential thrombocythemia myelofibrosis; 21% had received RBC transfusions within 8 weeks of study enrollment in the study. The median hemoglobin count was 10.4 g/dL and the median platelet count was 236 x 10^9/L. Patients had a median palpable spleen length of 15 cm below the costal margin, with 70% having a spleen length of 10 cm or more below the costal margin. The median spleen volume was 2,381 cm^3 (range, 451-7,765 cm^3). The investigators selected the best available therapy on a patient-by-patient basis. In the best available therapy arm, the medications received by more than 10% of patients were hydroxyurea (47%) and glucocorticoids (16%).

In the double-blind study, a 35% or greater reduction in spleen volume at 24 weeks occurred in 41.9% of ruxolitinib patients, compared with 0.7% of placebo patients ($P < .0001$). In the open-label study, a 35% or greater reduction in spleen volume at 48 weeks occurred in 28.5% of ruxolitinib patients, compared with 0% of patients in the best available care group ($P < .0001$). A secondary end point of the double-blind trial was a 50% or greater reduction in symptom score at 24 weeks as measured by the modified Myelofibrosis Symptom Assessment Form v2.0 diary (a daily diary measuring abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain, and early satiety). A 50% reduction in symptom score occurred in 45.9% of ruxolitinib patients, compared with 5.3% of placebo patients ($P < .0001$).

In the double-blind trial, 11.0% of ruxolitinib patients and 10.6% of placebo patients discontinued study treatment because of adverse events. In that trial, the most

How I treat myelofibrosis

The treatment of primary myelofibrosis hinges on the use of the allogeneic stem-cell transplant (see Commentary p. 176). First and foremost, one must obtain the correct diagnosis because several hematological malignancies can lead to a fibrotic marrow. At my institution, we use the World Health Organization's criteria to distinguish between myeloproliferative neoplasms. After the proper diagnosis, we risk stratify using the DIPSS (Dynamic International Prognostic Scoring System), which identifies patients as having low-, intermediate-1−, intermediate-2−, or high-risk disease. Patients with intermediate-2− and high-risk primary myelofibrosis have a median survival of about 2.9 and 1.3 years respectively, so we offer them an allogeneic transplant for curative purposes. In our transplant program, we have set forth restrictions on the use of the allogeneic transplant based on the hematopoietic cell transplantation comorbidity index (HCT-CI); age; and the patient's social support system, which is crucial for a successful outcome. We have noted that patients who are older than 60 years have about a 50% chance of nonrelapse mortality, and the outcomes in patients who are older than 65 seem to be even more bleak. Thus, the appropriate selection of the patient for an allogeneic transplant is critical for successful outcome.

Although this is a carefully selected population, the results from the use of an allogeneic stem-cell transplant in patients with primary myelofibrosis are quite dismal. The Center for International Bone Marrow Transplant Research has reported a nonrelapse mortality of 27% at 1 year and 35% at 5 years. The results were even worse in patients in the unrelated donor setting, with a mortality of 43% at 1 year and 50% at 5 years. The overall survival and both of these settings was about 30%-35%. One could argue that this data was collected before the era of allogeneic transplantation with reduced-intensity conditioning; however, the results of a reduced-intensity conditioning compared with a myeloablative conditioning regimen are fairly similar in terms of overall survival. Nevertheless, in patients older than 55 years, it is reasonable to suggest a reduced-intensity conditioning allogeneic transplantation. In my experience, the MD Anderson reduced toxicity, myeloablative regimen using fludarabine and targeted intravenous busulfan followed by the infusion of donor cells is an excellent strategy.

For patients with low- or intermediate-1−risk primary myelofibrosis, I use therapy with hydroxyurea and aspirin for a thrombocytosis of more than 1 million cells/mm^3. Splenectomy should be offered to patients who have significant discomfort or frequent transfusion needs. If the patient is at high risk for surgical splenectomy, then one might consider using the recently approved JAK inhibitor, ruxolitinib.

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common nonhematologic adverse events in patients who received ruxolitinib compared with those who received placebo were bruising (23.2% vs 14.6%, respectively placebo), dizziness (18.1% vs 7.3%), headache (14.8% vs 5.3%), urinary tract infection (9.0% vs 5.3%), weight gain (7.1% vs 1.3%), flatulence (5.2% vs 0.7%), and herpes zoster (1.9% vs 0.7%). In ruxolitinib patients, grade 3 adverse events consisted of bruising, dizziness, and weight gain in 0.6% each. In placebo patients, grade 3 urinary tract infection and weight gain occurred in 0.7% of patients each, and grade 4 urinary tract infection occurred in 0.7%. Alanine transaminase (ALT) abnormalities were more common in ruxolitinib patients than in controls (25.2% vs 7.3%, respectively), as were aspartate aminotransferase (AST) abnormalities (17.4% vs 6.0%) and cholesterol abnormalities (16.8% vs 0.7%). No grade 3 or grade 4 abnormalities were observed, except for grade 3 elevations in ALT in 1.3% of ruxolitinib patients. With regard to hematologic adverse events, thrombocytopenia occurred in 69.7% of ruxolitinib patients, including grade 3 and grade 4 events in 9.0% and 3.9%, respectively, compared with 30.5% of placebo patients, including grade 3 events in 1.3%. Anemia occurred in 96.1% of ruxolitinib patients, including grade 3 and grade 4 events in 34.2% and 11.0%, respectively, compared with 86.8% of placebo patients, including grade 3 and grade 4 events in 15.9%

and 3.3%, respectively. Neutropenia occurred in 18.7% of ruxolitinib patients, including grade 3 and grade 4 events in 5.2% and 1.9%, respectively, compared with 4.0% of placebo patients, including grade 3 and grade 4 events in 0.7% and 1.3%, respectively.

Withdrawal effects in long-term use

Tefferi and colleagues have reported on long-term outcomes and withdrawal effects in 51 patients who were treated at the Mayo Clinic as part of a phase I/II trial of ruxolitinib in myelofibrosis.[2,3] Of the 51 patients (enrolled from October 2007 through February 2009 and followed through July 2011 at the most recent reporting), 47 (92%) have discontinued treatment. The median time on treatment was 9.2 months. Discontinuation rates at 1, 2, and 3 years were 51%, 72%, and 89%, respectively, and were due to loss or lack of response or disease progression (34% of patients), toxicity with/without lack of response or disease progression (34%), patient/physician choice, often associated with lack of response (13%), and death during the study (4%).

Most of the patients experienced acute relapse of symptoms and splenomegaly during treatment discontinuation. Five patients (11%) required hospitalization after visits to the emergency department for acute relapse, rapid and painful enlargement of the spleen, and acute hemodynamic decompensation that occasionally led to a septic shock-like syndrome. At the time of reporting, 18 patients (35%) had died, and 5 (10%) had leukemic formations. There was no significant difference in survival rate between the 51 ruxolitinib-treated patients and a cohort of 410 patients with primary myelofibrosis who were treated with standard therapy at the Mayo Clinic in the most recent 10-year period. Tefferi and colleagues have noted that their experience calls for full disclosure of the ruxolitinib withdrawal syndrome to patients with myelofibrosis before ruxolitinib therapy is initiated, and they urge that the discontinuation of treatment should be performed under close physician supervision and preferably in a tapered schedule.[2]

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