How I treat myelofibrosis

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Myelofibrosis (MF) is a BCR-ABL1–negative myeloproliferative neoplasm characterized by clonal myeloproliferation, dysregulated kinase signaling, and release of abnormal cytokines. In recent years, important progress has been made in the molecular biology and the prognostic assessment of MF. Conventional treatment has limited impact on the patients’ survival; it includes a wait-and-see approach for asymptomatic patients, erythropoiesis-stimulating agents, androgens, or immunomodulatory agents for anemia, cytoxicreduction drugs such as hydroxyurea for the splenomegaly and constitutional symptoms, and splenectomy or radiotherapy in selected patients. The discovery of the Janus kinase (JAK)2 mutation triggered the development of molecular targeted therapy of MF. The JAK inhibitors are effective in both JAK2-positive and JAK2-negative MF; one of them, ruxolitinib, is the current best available therapy for MF splenomegaly and constitutional symptoms. However, although ruxolitinib has changed the therapeutic scenario of MF, there is no clear indication of a disease-modifying effect.

Allogeneic stem cell transplantation remains the only curative therapy of MF, but due to its associated morbidity and mortality, it is usually restricted to eligible high- and intermediate-2–risk MF patients. To improve current therapeutic results, the combination of JAK inhibitors with other agents is currently being tested, and newer drugs are being investigated.

How I treat anemia

Case study 1

A 51-year-old woman was diagnosed with ET after the incidental discovery of thrombocytosis, with the marrow biopsy being...
Anemia is the more frequent manifestation of MF, being due to decreased bone marrow production, ineffective erythropoiesis, hypersplenism, and occasional bleeding. Dilution by the increased plasma volume secondary to splenomegaly can contribute. Sometimes, iron, vitamin B₁₂, or folate deficiency is found, whereas autoimmune hemolysis is rare. The anemia is often accentuated by the cytoreductive agents or the JAK inhibitors.

I always start studying the anemia of MF by excluding treatable causes, such as iron, folate, or vitamin B₁₂ deficiency, which are infrequent. When there is marked hemolysis, I perform a Coombs’ test because, if positive, corticosteroids are the therapy of choice, but this is exceedingly rare. Most patients require an anemia-treating agent. Hb < 10 g/dL is the threshold usually triggering treatment institution, but there are individual variations. Thus, an elderly person with cardiac failure may need treatment with an Hb of 10.5 g/dL, whereas a younger patient may tolerate values of 9 to 10 g/dL. Therapeutic options include erythropoiesis-stimulating agents (ESAs), androgens, immunomodulators, splenectomy, and prednisone. Figure 2 shows my therapeutic algorithm for the anemia of MF, in which the initial choice between ESA and danazol is based on the patient’s serum erythropoietin (Epo) levels.

ESAs

With recombinant human Epo or darbepoetin-α, anemia responses (transfusion independence with normal Hb, transfusion decrease > 50%, or sustained Hb increase > 2 g/dL in non–transfusion-dependent patients) are achieved in 23% to 60% of patients. Median duration of responses is 12 months, and half are long lasting; they are usually restricted to patients with inadequate Epo levels (≤ 125 mU/mL), being less frequent in those with large spleens or transfusion dependence. I start with a weekly dose of 20,000 U of recombinant human Epo or 150 μg of darbepoetin-α, and I double the dose if no response is observed after 4 weeks. If there is no response at 3 months, therapy should be stopped. A spleen increase can be seen with ESA treatment.

Androgens

Nandrolone, fluoxymesterone, methandrostenolone, and oxymetholone improve anemia in 30% to 60% of patients. Factors associated with a favorable response are female gender, previous splenectomy or lack of huge splenomegaly, and normal karyotype. Similar results, with less toxicity, are obtained with danazol, a semisynthetic attenuated androgen that can also correct thrombocytopenia. Responses approach 40%. Before starting danazol, men must be asked for prostatic symptoms, and serum prostate-specific antigen levels must be determined to rule out prostate cancer. Dose must be sufficient (600 mg daily) and should be maintained for ≥ 6 months, because most responses are seen between 3 and 6 months. Then, it must be progressively reduced to the minimum necessary dose to maintain response, usually 200 mg/day. Hepatic alterations are the main toxicity; they appear in < 20% of patients and are generally moderate, requiring dose reduction but rarely definitive discontinuation of the drug. The patient’s liver function must be monitored at every visit, and ultrasound imaging must be performed annually to exclude appearance of liver tumors; men must be periodically screened for prostate cancer.

Immunomodulating drugs

Thalidomide, at 100 to 200 mg/day, is associated with high withdrawal due to side effects such as constipation, fatigue, paresthesias, sedation, hematologic toxicity, and myeloproliferative acceleration; anemia response is 29%. To minimize toxicity, lower doses (50 mg daily) are given in combination with oral prednisone (0.5 mg/kg daily for 3 months and then taper), resulting in less withdrawal and...
similar response rates. The efficacy of this combination has been described as secondary to prednisone, because following its discontinuation, many responses are lost.

Lenalidomide produces 22% anemia responses and 10% to 42% responses in splenomegaly. Dose is 5 to 10 mg daily (depending on platelet count) for 3 weeks, every 4 weeks. Withdrawal is high because of side effects, mainly hematologic toxicity. To reduce toxicity, lenalidomide has been combined with a low-dose prednisone taper; in one study, anemia response increased to 30%, but in another, it was 19%. Lenalidomide is the choice treatment of the rare cases of MF with 5q deletion.

Pomalidomide, a less toxic immunomodulator, showed promise in a phase 2 study. However, a phase 3 study in transfusion-dependent patients failed to show significant differences with placebo.

Splenectomy

Splenectomy can be considered in patients with transfusion-dependent anemia refractory to drug therapy, but the procedure involves substantial risk. Indeed, in a large series, perioperative morbidity was 31% and mortality was 9%. The main complications are bleeding (especially hemoperitoneum), infections, and thrombosis, primarily in the splanchic veins. Massive hepatomegaly due to compensatory myeloid metaplasia develops in 16% to 24% of patients, some of whom may die of liver failure. Durable responses in transfusion-dependent anemia are 23%. The decision on splenectomy should be taken carefully, balancing the risks against the possible benefits. Splenectomy is the choice treatment of MF-associated immune hemolysis unresponsive to corticosteroids.

Corticosteroids

I use prednisone for palliation of anemia if the abovementioned drugs fail and the patient is not a good candidate for allo-SCT or splenectomy. I start with 30 mg daily, which I reduce to 15 to 20 mg after a few weeks. Hb increases of 1 to 2 g/L are often seen, which can be sufficient to improve patient well-being.

Iron chelation?

A substantial proportion of MF patients require red blood cell transfusions, but there is no data supporting the value of iron chelation therapy. Given the short survival associated with transfusion dependency, I restrict iron chelation to potential candidates for transplantation.

How I treat splenomegaly

Case study 2

A 64-year-old woman was diagnosed with PMF after several months of abdominal discomfort. The spleen was palpable at 12 cm below costal margin. Hb was 11.2 g/dL, leukocyte count was 14 × 10^9/L, with leukoerythroblastosis and no blasts, and platelet level was 486 × 10^9/L. Bone marrow cytogenetic study was normal, and marrow biopsy showed clusters of dysplastic megakaryocytes with marked reticulin fibrosis, corresponding to MF-2 of the World Health Organization histological grading. The JAK2 and MPL mutations were negative, and the patient was recently found to have a 52-bp deletion of CALR. Hydroxyurea was instituted, resulting in marked spleen reduction and disappearance of symptoms. However, progressive splenomegaly was observed over time despite increasing hydroxyurea dose. The patient refused splenectomy, and splenic radiation was performed, but it had to be interrupted due to pan-cytopenia. When hematologic values recovered, the patient went back to hydroxyurea, with poor control of the splenomegaly and symptoms. Once it was available, I started ruxolitinib.

Splenomegaly is a characteristic feature of MF, being due to extramedullary hematopoiesis that frequently also affects the liver. Despite its clinical relevance, it has not been a prognostic factor in most studies, because it is usually associated with other poor prognosis factors. Symptoms from splenomegaly correlate with spleen size. Thus, moderate splenomegaly may not produce symptoms, but, as spleen increases, it causes important abdominal symptoms, often with constitutional symptoms, accentuation of the cytopenias, and signs of portal hypertension.

It is generally agreed that a wait-and-see approach is a reasonable option in patients with moderate and asymptomatic splenomegaly, with therapy being delayed until appearance of symptoms, especially considering that treatment may worsen the cytopenias. This is my approach. However, some authors have called for earlier treatment in asymptomatic patients, mainly with interferon-α, which has been shown to achieve disease stability or improvement and occasional fibrosis reversal. Nevertheless, sooner or later, all patients will require therapy. Conventional modalities include cytoreductive drugs, splenectomy, and splenic radiation. The JAK inhibitors have changed this scenario.

Cytoreductive drugs

Hydroxyurea was for many years the choice therapy for MF splenomegaly. My starting daily dose is 500 mg, which I escalate depending on response and tolerability. With increasing doses, accentuation of anemia, requiring anemia-alleviating drugs, is often seen. Oral or leg ulcers are the most characteristic nonhematologic toxicity of hydroxyurea, which is usually associated with prolonged administration and high doses. The overall response is 40%, and median duration is 13.2 months. Therefore, at roughly 1 year of hydroxyurea start, 80% of patients require an alternative therapy. Moreover, the responses are not comparable with those of JAK inhibitors. However, hydroxyurea can be an option for moderately symptomatic splenomegaly, especially in the setting of difficult access to JAK inhibitors. Other drugs such as busulfan or melphalan are rarely used.

Splenectomy

Splenectomy may be indicated for large and painful splenomegaly refractory to drug therapy. As previously mentioned, the decision must be individualized due to the associated risks. Although the availability of JAK2 inhibitors has reduced the use of splenectomy in MF, it can be considered in eligible patients resistant to these drugs.

Radiation therapy

Splenic radiation, on a fractionated basis, at a daily dose of 0.4 to 1 Gy, with weekly evaluation of spleen size and hematologic values until therapeutic effect is achieved or hematological toxicity develops, can be applied to patients that are refractory to JAK2 inhibitors and poor candidates to surgery. In one series, median total dose per course was 9.8 Gy (range, 0.6-30.05 Gy). However, its benefit is transient, whereas, due to the effect on circulating progenitors, it involves the risk of severe and prolonged cytopenias, developing in one-third of patients. Therefore, I do not recommend routine use of splenic radiation; JAK inhibitors have further reduced the use of this therapy.
Ruxolitinib and other JAK2 inhibitors

The discovery of the JAK2 mutation triggered development of molecular targeted therapies for MF. These agents mainly inhibit dysregulated JAK-STAT signaling, present in all patients irrespective of JAK2 mutational status. All have overlapping activity against other members of the JAK family (including JAK1, JAK2, JAK3, and Tyk2) and sometimes against other tyrosine kinases. Unlike the BCR-ABL1 inhibitors, the JAK inhibitors are not selective for mutated JAK2, which explains their efficacy in JAK2-positive and JAK2-negative MF and their hematologic toxicity, given the importance of the JAK-STAT pathway in hematopoiesis. Table 1 shows a summary of the JAK2 inhibitors tested in MF.

Ruxolitinib, an oral JAK1/JAK2 inhibitor, is the first agent approved for the treatment of MF. In the phase 1-2 trial, it was well tolerated, with thrombocytopenia as the dose-limiting toxicity. Spleen reduction and control of symptoms were usually dramatic but also drug and dose dependent, because drug discontinuation or reduction was followed by rapid spleen increase and reappearance of symptoms. Ruxolitinib is also effective in MF-associated hepatomegaly. Normalization of several proinflammatory cytokines correlates with symptomatic improvement, with this being ascribed to the drug anti-JAK1 activity. Sudden ruxolitinib withdrawal has been reported to provoke a shock-like syndrome due to reemergence of the suppressed cytokines. Although this complication was not observed in the phase 3 studies, abrupt interruption of ruxolitinib was seen in 2% of patients treated for 3 years of treatment. Occasional reactivation of tuberculosis and other opportunistic infections has also been reported, being attributed to continuous suppression of T lymphocytes. However, this complication is anecdotal among the many patients currently receiving the drug worldwide.

In the phase 3 studies, ruxolitinib dose was 15 or 20 mg twice daily, depending on platelet counts (100-200 × 10⁹/L or >200 × 10⁹/L). To minimize the negative effect on anemia, I start with 10 mg twice daily in patients without massive splenomegaly and with moderate symptoms, and I escalate the dose depending on the response achieved. A recent study in patients with moderate thrombocytopenia (from 50 × 10⁹/L to 100 × 10⁹/L) has shown the feasibility of starting with 5 mg twice daily and then escalating to 10 mg (and occasionally to 15 mg) twice daily, without causing severe thrombocytopenia.

Treatment should be stopped if platelets fall below 50 × 10⁹/L. In case of renal or liver function impairment, I start with a dose of 10 mg twice daily. With regard to treatment duration, I definitively stop therapy if there is no clinically meaningful response after 6 months. In this sense, although no specific criteria for ruxolitinib failure are available, I consider the response unsatisfactory when spleen reduction is inferior to 25% of the baseline value (by palpation) and constitutional symptoms persist. The recently developed scale for symptom assessment in patients with MPNs can help in evaluating the impact of therapy on MF-associated symptoms. With certain frequency, ruxolitinib is unable to control leukocytosis or thrombocytosis; if there is clear benefit in spleen and symptoms, I consider adding hydroxyurea.

Despite its dramatic symptomatic improvement and the suggestion of survival prolongation, there is no clear indication of a disease-modifying effect of ruxolitinib. Besides, at 3 years, 60% of patients are off treatment. Therefore, further efforts are necessary to improve ruxolitinib results. This is currently being attempted by combination with anemia-alleviating drugs or with agents aimed at achieving deeper disease-modifying effect (Table 2). Other JAK inhibitors that selectively suppress the clonal cells and restore normal hematopoiesis need to be developed.

Fedratinib (SAR302503), a preferential JAK2 inhibitor, has recently been withdrawn due to occurrence of Wernicke’s encephalopathy in some patients.

Momelotinib (CYT3879), a JAK1/JAK2 inhibitor, produced 45% spleen responses, with frequent improvement in constitutional symptoms. Among patients evaluable for anemia response, 50%
Table 3. Current prognostic models for MF

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPSS</th>
<th>DIPSS</th>
<th>DIPSS-plus</th>
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<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Hb &lt; 10 g/dL</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Leukocytes &gt; 25 × 10^9/L</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Blood blasts ≥ 1%</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Platelets &lt; 100 × 10^9/L</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Red blood cell transfusion need</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>UNFAVORABLE KARYOTYPE (+8, −7/7q−, −5/5q-, 17q, 12p-, 11q23 rearrangement)</td>
<td>1 point each</td>
<td>1 point each (Hb: 2 points)</td>
<td>The sum of the patient’s DIPSS score (int-1: 1 point; int-2: 2 points; high: 3 points) plus 1 additional point for each of the following: platelets &lt; 100 × 10^9/L; unfavorable karyotype; transfusion need</td>
</tr>
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IPSS: low risk, 0 points; intermediate-1 risk, 1 point; intermediate-2 risk, 2 points; high risk, 3 to 5 points; DIPPS: low risk, 0 points; intermediate-1 risk, 1 to 2 points; intermediate-2 risk, 3 to 4 points; high risk, 5 to 6 points; DIPPS-plus: low risk, 0 points; intermediate-1 risk, 1 point; intermediate-2 risk, 2 to 3 points; high risk, 4 to 6 points.

responded, including 58% with transfusion dependence. Grade 3-4 thrombocytopenia appeared in 25% of patients; hyperlipasemia and headache were the most characteristic nonhematologic adverse effects. A phase 3 study comparing momelotinib with ruxolitinib is in progress.

Pacritinib (SB1518), a selective JAK2 inhibitor, reduced splenomegaly in 57% of patients, with scarce myelosuppression and some gastrointestinal side effects. A phase 3 study is also ongoing.

The approval of ruxolitinib has led to its incorporation into MF treatment algorithms as the best available therapy for splenomegaly and/or constitutional symptoms. Quite likely, other JAK2 inhibitors will follow. The trade-offs between clinical activity and toxicity will help choosing the right drug. Longer follow-up is required to establish the definitive role of JAK inhibitors in MF; information on nonhematologic long-term effects is also needed.

How I decide on transplantation

Case study 3

A 57-year-old woman was diagnosed with JAK2-positive PMF after several months of weight loss, night sweats, fatigue, and abdominal pain. Spleen and liver were palpable at 14 and 6 cm below the costal margin. Hb was 9.6 g/dL, WBC count was 28 × 10^9/L, with leukoerythroblastosis and 5% blasts, platelet count was 520 × 10^9/L, and lactate dehydrogenase level was 1834 U/L. Trisomy 8 and marked fibrosis were found in the bone marrow. Hydroxyurea was started, with a rapid reduction of splenomegaly and leukocytosis, disappearance of symptoms, and improvement in the general condition. The patient had a compatible brother and, because she had high-risk PMF by both the International Prognostic Scoring System (IPSS) and dynamic IPSS (DIPSS)-plus (that considers also the unfavorable karyotype), I decided to proceed to allo-SCT.

Median survival of PMF currently approaches 7 years. Survival is heterogeneous, with some patients living for >20 years and others dying within 1 or 2 years. Prognosis at presentation is assessed using the IPSS, based on 5 poor prognostic factors: age ≥65 years, constitutional symptoms, Hb <10 g/dL, leukocytes >25 × 10^9/L, and blood blasts ≥1%. They allow recognizing 4 prognostic groups (low, intermediate-1, intermediate-2, and high risk), with median survival around 11, 8, 4, and 2 years, respectively. The IPSS has been complemented by DIPSS, based on the same factors but giving higher weight to anemia, for its use during the evolution. Of note, sometimes the DIPSS is not used correctly, when applied at presentation. The IPSS was derived from 1054 patients and, although Hb <10 g/dL was the main prognostic factor, its prognostic weight was slightly higher than that of the other factors; therefore, 1 point was assigned to the 5 factors. The DIPSS was derived from the IPSS series but using half of patients; therefore, these results cannot substitute those obtained from the whole series. Acquiring an Hb <10 g/dL during the evolution had double prognostic impact than acquisition of the other factors; because of this, 2 points were assigned to anemia. In summary, the IPSS must be applied at presentation and the DIPSS during the evolution. The DIPSS has been refined into a DIPSS-plus model, also including thrombocytopenia, transfusion need, and karyotype. Table 3 summarizes current PMF prognostic models. Although the 3 models were derived from PMF patients, they are also applied to post-ET and post-PV MF. However, recent data in this setting indicate that, although the IPSS would be useful to identify high-risk patients, it would not accurately discriminate between the other risk categories. The lack of prognostic significance of some of the IPSS variables (notably, the leukocyte count) in these patients might be ascribed to the effect of the cytoreductive therapy that many were receiving for ET or PV at time of myelofibrotic transformation.

Recently, advances have been made in molecular prognostication of PMF. Concerning MPN phenotype driver mutations, there is no agreement on the prognostic value of the JAK2 mutation or its allelic rearrangement 2 mutation or its allelic rearrangement 2 mutation or its allelic...
How I treat special situations

Portal hypertension can develop in MF as a consequence of increased splenic blood flow, myeloid metaplasia of the liver, and splanchnic vein thrombosis. In addition to the general measures for portal hypertension, splenectomy can be considered in selected patients. Favorable results have been reported with the use of ruxolitinib in this setting.82

Low-dose radiation is the choice treatment of symptomatic extramedullary hematopoiesis in sites other than spleen and liver83 and for MF-associated pulmonary hypertension.84

Thrombosis is a complication of MF85,86 appearing in ~7% of patients; predisposing factors are older age, presence of JAK2 mutation, and leukocytosis.86 Given the competing risk of death from other complications, unlike in PV and ET, thrombosis is not a major issue in MF. Because of this, the use of antithrombotic therapy to prevent thrombosis is not clearly recommended. In my practice, as long as platelets remain high, I maintain low-dose aspirin in patients with post-ET or post-PV MF who were receiving such therapy for ET or PV. In PMF, I prescribe antithrombotic treatment only in patients with a history of ischemic events.

Blast phase of MF has an especially poor prognosis, with a median survival of ~2 months.87 In subjects <70 years of age, I administer acute myeloid leukemia-like chemotherapy with the aim of achieving a favorable response that allows transplantation. With such an approach, 20% to 45% of selected patients were finally transplanted, and half remained alive at 2 years.88 However, the majority of patients are candidates for palliative therapy only, based in my practice on transfusion support and oral mercaptourine. New options, such as the JAK inhibitors and the hypomethylating agents, are being investigated.

Conclusions and future directions

Despite recent advances, for most MF patients, treatment remains unsatisfactory. Newer drugs are being tested (Table 4), but, because of space constraints, they have not been discussed here. Some will be withdrawn, but others will be incorporated into the MF therapeutic armamentarium. Therefore, my management of MF patients also includes enrollment into clinical trials in the hope that this will lead to the availability of drugs able to modify the disease natural history.

Acknowledgment

This study was supported in part by Instituto de Salud Carlos III, Spanish Ministry of Health grant RD012/0036/0004.

Authorship

Contribution: F.C. wrote the paper.

Conflict-of-interest disclosure: F.C. is a consultant for Novartis, Sanofi-Aventis, Gilead, and CTI-Baxter.

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