How I treat myelofibrosis

By

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Abstract

Myelofibrosis (MF) is a BCR/ABL-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 knowledge of 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, cytoreductive drugs such as hydroxyurea for the splenomegaly and constitutional symptoms, and splenectomy or radiotherapy in selected patients. The discovery of the JAK2 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. In order to improve current therapeutic results, the combination of JAK inhibitors with other agents is currently being tested and newer drugs are being investigated.
Introduction

Myelofibrosis (MF), formerly known as idiopathic myelofibrosis, myelofibrosis with myeloid metaphasia or agnogenic myeloid metaphasia, is one of the classical BCR/ABL-negative chronic myeloproliferative neoplasms (MPN), a group also including essential thrombocytemia (ET) and polycythemia vera (PV) (1). Either appearing de novo (primary myelofibrosis or PMF) or following a previous ET or PV (post-ET or post-PV MF) (2), the disease is essentially the same. MF is a clonal proliferation of a pluripotent hematopoietic stem cell (3) in which the abnormal cell population releases several cytokines and growth factors in the bone marrow that lead to marrow fibrosis and stroma changes, and colonizes extramedullary organs such as the spleen and liver (4). Discovery of the V617F mutation of the JAK2 gene in 60% of patients with PMF or post-ET MF and 95% of those with post-PV MF represented an important step in the understanding of the pathogenesis of MF (5-7). Mutations in the thrombopoietin receptor gene (MPL) were subsequently found in 3-8% of patients with PMF and post-ET MF (8), whereas mutations in the calreticulin gene (CALR) have been observed in half of patients with PMF and post-ET MF lacking JAK2 and MPL mutations (9, 10). Mutations shared by other myeloid neoplasms are found in some patients (11). However, the genetic trigger of MF is unknown.

MF mostly affects elderly people. At present, there is no curative treatment other than allogeneic hemopoietic stem cell transplantation (allo-SCT), which can be applied to a minority of patients. Therefore, treatment remains essentially palliative and aimed at controlling disease symptoms and complications and improving the patients’ quality of
life. The therapeutic landscape of MF has changed with the introduction of the JAK inhibitors.

In the present article, I will discuss the treatment options currently available for MF, how I have incorporated the new prognostic information to the clinical decision-making process, and how I have integrated novel therapeutic modalities in my practice. The discussion on the more relevant clinical scenarios of MF will be preceded by a representative case study to illustrate how I decide the treatment strategy for the main clinical situations of this complex disease.

The clinical picture of myelofibrosis

The clinical manifestations of MF are heterogeneous (figure 1). Up to 30% of patients are initially asymptomatic; most patients present with symptoms from anemia or splenomegaly, or constitutional symptoms. As the disease evolves, all patients become symptomatic due to marrow failure, increasing splenomegaly causing abdominal symptoms and early satiety, and constitutional symptoms such as weight loss, night sweats, and low-grade fever. Aquagenic pruritus, bone pain, or thrombosis may be a problem. In the advanced phases, extramedullary hematopoiesis in sites other than the spleen and liver can be seen. Evolution to acute myeloid leukemia can be observed.

Since current therapies other than allo-SCT are not able to control all clinical manifestations of MF, treatment choice is mainly guided by the main symptom or feature. However, the situation is often more complex, because patients may have
several symptoms and a therapy instituted for one can worsen another, as it is the case of anemia, frequently accentuated by the therapy for splenomegaly.

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 normocellular and showing proliferation of megakaryocytes, most of them with hyperlobulated nuclei, with absent fibrosis. The patient remained asymptomatic without treatment for eight years, when spontaneous platelet normalization was noted, with Hb decrease, dacryocytes in blood, slight leukocytosis with leukoerythroblastosis, and increased serum LDH. Spleen was not palpable. V617F JAK2 mutation was negative and mutation W515L of the MPL gene was found. Bone marrow biopsy confirmed post-ET myelofibrosis. Serum ferritin, vitamin B12, and folate were normal. Since anemia was mild and well tolerated, no treatment was instituted. However, one year later, the patient started complaining of fatigue. A spleen tip was palpable. Hb was 9.4 g/dL, without other changes in blood. I had to decide upon the most appropriate treatment for the patient.

Fatigue is a common symptom in MF (13). Its main cause is anemia, but it can also be due to the disease activity itself, especially in patients with constitutional symptoms and signs of hyperproliferation. A role for the abnormal expression of several proinflammatory cytokines in the fatigue of MF patients has been pointed out (14). This patient did not have any of the above-mentioned features and fatigue appeared
coincidently with the accentuation of anemia. Therefore, she needed treatment for the anemia.

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, while autoimmune hemolysis is rare (15). 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 since, 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 a Hb of 10.5 g/dL, while a younger patient may tolerate values of 9 to 10 g/dL. Therapeutic options include erythropoiesis-stimulating agents (ESA), 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.

**Erythropoiesis-stimulating agents (ESA)**

With recombinant human erythropoietin (rHuEPO) 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
23-60% of patients (16-18). 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) (16-18), being less frequent in those with large spleens or transfusion dependence (16-19). I start with a weekly dose of 20,000 U of rHuEPO 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 three months, therapy should be stopped. Spleen increase can be seen with ESA treatment.

Androgens

Nandrolone, fluoxymesterone, methandrostenolone, and oxymetholone improve anemia in 30-60% of patients (20, 21). Factors associated with a favorable response are female sex, 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 (22). Responses approach 40% (22). Before starting danazol, men must be asked for prostatic symptoms and serum PSA levels determined to rule out prostate cancer. Dose must be sufficient (600 mg daily) and should be maintained for at least 6 months, since 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 less than 20% of patients and are generally moderate, requiring dose reduction but rarely definitive discontinuation of the drug. Patient’s liver function must be monitored at every visit and ultrasound imaging performed annually to exclude appearance of liver tumors; males must be periodically screened for prostate cancer.
Immunomodulating drugs

Thalidomide, at 100-200 mg/day, is associated with high withdrawal due to side effects such as constipation, fatigue, paresthesiae, sedation, hematologic toxicity, and myeloproliferative acceleration (23); 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 three months and then taper), resulting in less withdrawal and similar response rates (24). The efficacy of this combination has been ascribed to prednisone, since following its discontinuation many responses are lost (25).

Lenalidomide produces 22% anemia responses and 10-42% responses in splenomegaly (26-28). Dose is 5-10 mg daily (depending on platelet count) for three weeks, every four weeks. Withdrawal is high because of side effects, mainly hematologic toxicity (26). To reduce toxicity, lenalidomide has been combined with low-dose prednisone taper; in one study, anemia response increased to 30% (27) but in another it was 19% (28). Lenalidomide is the choice treatment for the rare cases of MF with 5q deletion (29).

Pomalidomide, a less toxic immunomodulator, showed promise in a phase 2 study (30). However, a phase 3 study in transfusion-dependent patients failed to show significant differences with placebo (31).

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 9% (32). Main
complications are bleeding (especially hemoperitoneum), infections, and thrombosis, primarily in the splanchnic veins (33). Massive hepatomegaly due to compensatory myeloid metaplasia develops in 16-24% of patients, some of whom may die from liver failure (34). Durable responses in transfusion-dependent anemia are 23% (33). The decision on splenectomy should be taken carefully, balancing the risks against the possible benefits. Splenectomy is the choice treatment for MF-associated immune hemolysis unresponsive to corticosteroids.

Corticosteroids

I use prednisone for palliation of anemia if the above-mentioned 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 15-20 mg after some weeks. Hb increases of 1-2 g/L are often seen, which can be sufficient to improve the patients’ wellbeing.

Iron chelation?

A substantial proportion of MF patients require RBC transfusions, but there are no data supporting the value of iron chelation therapy (35). 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. Spleen was palpable at 12 cm below costal margin. Hb was 11.2 g/dL, WBC count was 14 x10^9/L, with leukoerythroblastosis and no blasts, and platelets 486 x10^9/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 WHO histological grading. The JAK2 and MPL mutations were negative and the patient was recently found to have a 52bp 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 pancytopenia. When hematologic values recovered, 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 (36) that frequently also affects the liver. Despite its clinical relevance, it has not been a prognostic factor in most studies, since it is usually associated with other poor prognosis factors (12). 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 (37-39). 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 non-hematologic toxicity of hydroxyurea, being usually associated with prolonged administration and high doses. Overall response is 40% and median duration 13.2 months (40). Therefore, at roughly one 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 employed (41).

**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 fractioned 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 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 (43), it involves the risk of severe and prolonged cytopenias, developing in one third of patients (44). 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 signalling, present in all patients irrespective of JAK2 mutational status (45). 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/ABL inhibitors, the JAK inhibitors are not selective for mutated JAK2 (46), 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 (47). Spleen reduction and control of symptoms were usually dramatic
but also drug- and dose-dependent, since 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 pro-inflammatory 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 re-emergence of the suppressed cytokines (48). Although this complication was not observed in the phase 3 studies, abrupt interruption of ruxolitinib must be avoided and the drug tapered, combined with prednisone taper. In most patients, accentuation of anemia is observed, especially during the first months of treatment.

Two phase-3 studies, in patients with intermediate-2 and high-risk MF, compared ruxolitinib with placebo (COMFORT-I) (49) or best-available therapy (COMFORT-II) (50). In both studies, ruxolitinib achieved the primary endpoint of > 35% reduction in spleen size, by imaging techniques, at 24 or 48 weeks of treatment, respectively. Based on these results, ruxolitinib was approved in USA for patients with high- or intermediate-risk MF and in Europe for splenomegaly and/or constitutional symptoms irrespective of the risk group, which makes more sense. Response was independent of the JAK2 mutational status, without differences between PMF and post-ET/PV MF. With longer follow-up, the effect on JAK2V617F allele burden has been modest (51). Concerning the effect on marrow fibrosis, a patient has been reported in whom complete resolution of fibrosis was observed after three years of treatment (52). In the phase 1 and 2 ruxolitinib trials, at five years, improvement in fibrosis was seen in 36% of patients, whereas in the majority no significant histological changes were observed (53). Longer follow-up will allow determine whether prolonged
ruxolitinib administration could increase the proportion of patients achieving fibrosis improvement or resolution. Historical comparison of ruxolitinib-treated patients with matched MF populations has shown a survival advantage for the former (54, 55). Moreover, despite the crossover, extended follow-up of the COMFORT studies indicates a survival advantage for patients assigned to ruxolitinib (51, 55).

An increase in urinary tract infections has been noted under ruxolitinib (51). Occasional reactivation of tuberculosis and other opportunistic infections has also been reported (57-59), 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 x10^9/L or > 200 x10^9/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 x10^9/L to 100 x10^9/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 (60). Treatment should be stopped if platelets fall below 50 x10^9/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

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symptoms persist. The recently developed scale for symptom assessment in patients with myeloproliferative neoplasms can help in evaluating the impact of therapy on MF-associated symptoms (13). 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 three years, 60% of patients are off treatment (51). 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 (61). Momelotinib (CYT3879), a JAK1/JAK2 inhibitor, produced 45% spleen responses, with frequent improvement in constitutional symptoms (62). Among patients evaluable for anemia response, 50% responded, including 58% with transfusion dependence. Grade 3-4 thrombocytopenia appeared in 25% of patients; hyperlipasemia and headache were the most characteristic non-hematologic 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 (63). 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 non-hematologic long-term
effects is also needed.

How I decide on transplantation

Case study 3

A 57-year-old female 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 28 x10^9/L, with
leukoerythroblastosis and 5% blasts, platelet count 520 x10^9/L, and LDH 1834 U/L.
Trisomy 8 and marked fibrosis were found in bone marrow. Hydroxyurea was started,
with rapid reduction of splenomegaly and leukocytosis, disappearance of symptoms,
and improvement in the general condition. The patient had a compatible brother and,
since she had high-risk PMF by both the IPSS and DIPSS-plus (that considers also the
unfavorable karyotype) (12, 64), I decided to proceed to allo-SCT.

Median survival of PMF currently approaches 7 years (65). Survival is heterogeneous,
with some patients living for more than 20 years and others dying within one or two
years. Prognosis at presentation is assessed using the International Prognostic Scoring
System (IPSS), based on five poor prognostic factors: age over 65 years, constitutional
symptoms, Hb <10 g/dL, leukocytes >25 x10^9/L, and blood blasts >1%. They allow
recognizing four prognostic groups (low, intermediate-1, intermediate-2, and high risk), with median survival around 11, 8, 4, and 2 years, respectively (12). The IPSS has been complemented by a dynamic IPSS (DIPSS), based on the same factors but giving higher weight to anemia, for its use during the evolution (66). 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 five 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 a 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 (64). Table 3 summarizes current PMF prognostic models. Although the three models were derived from PMF patients, they are also applied to post-ET and post-PV myelofibrosis. However, recent data in this setting indicate that, while the IPSS would be useful to identify high-risk patients, it would not accurately discriminate between the other risk categories (67). 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 cytoreduceuctive 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 burden (68, 69), while MPL mutations do not seem to
be prognostically relevant (70). On the contrary, CALR mutations seem to be associated with better prognosis (71, 72). Of note, triple-negative patients (i.e., without JAK2, MPL, or CALR mutations) have a particularly poor outcome (71, 72). Quite likely, this information will soon be incorporated into MF prognostic assessment.

With regard to other molecular abnormalities, mutations in ASXL1, EZH2, IDH1/2, and SFSF2 are associated with poorer outcome (73), having been proposed for molecular prognostication of PMF (74). Of note, most patients with these mutations belonged to the intermediate-2 and high-risk groups, having therefore poor prognosis; however, roughly 20% of patients in the low and intermediate-1 groups also displayed some of these mutations. For now, presence of these alterations in the absence of other poor prognostic features is not sufficient to support the indication of intensive therapies such as allo-SCT. They can be considered as a warning, recommending the patient’s closer monitoring to detect early changes indicating the need for a different therapeutic strategy. In summary, this new information will require validation and consolidation before its routine incorporation into decision-making.

The main utility of prognostication in MF is to help decide on allo-SCT. Some authors claim for transplantation in all eligible patients, irrespective of the risk group (75, 76). However, given the associated mortality and morbidity (77), there is wide consensus on indicating allo-SCT in high-risk patients and not in low- and intermediate-1 risk MF (figure 3). Transplantation is also indicated for intermediate-2 risk patients. In this group, my personal approach is to perform allo-SCT in patients 60-year old or younger; over this age, given the procedure high mortality, I try drug therapy first and I go for transplantation in case of unsatisfactory response. Under 45-50 years, I use
myeloablative regimens with targeted busulfan and cyclophosphamide (78), whereas in older patients I use reduced-intensity conditioning with fludarabine and busulfan (79). In case of massive splenomegaly, I no longer perform splenectomy before transplantation; instead, I currently give JAK inhibitors to reduce tumor burden and to improve the general status (80-82). In good candidates for allo-SCT who improve under JAK inhibitors, I take advantage to proceed to transplantation in better general conditions and I do not postpone the procedure until response is lost, since this could jeopardize the success of transplantation.

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 (83).

Low-dose radiation is the choice treatment for symptomatic extramedullary hematopoiesis in sites other than spleen and liver (84) and for MF-associated pulmonary hypertension (85).

Thrombosis is a complication of MF (86, 87) appearing in about 7% of patients; predisposing factors are older age, presence of JAK2 mutation, and leukocytosis (87). 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 anti-platelet 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 myelofibrosis who were receiving such therapy for ET or PV. In PMF, I prescribe anti-platelet treatment only in patients with a history of ischemic events.

Blast phase of MF has an especially poor prognosis, with a median survival around 2 months (88). In subjects under 70, I administer acute myeloid leukemia-like chemotherapy with the aim to achieve a favorable response allowing transplantation. With such approach, 20-45% of selected patients were finally transplanted and half remained alive at 2 years (89). However, the majority of patients are candidates for palliative therapy only, based in my practice on transfusion support and oral mercaptopurine. 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 therapeutice armamentarium. Therefore, my management of MF patients also includes enrolment into clinical trials in the hope that this will lead to the availability of drugs able to modify the disease natural history.

Acknowledgement
This study has been supported in part by grant RD012/0036/0004 from the Instituto de Salud Carlos III, Spanish Ministry of Health.

Disclosures

F.C. was the single author of this manuscript.

Conflict-of-interest disclosure: The author is a consultant for Novartis, Sanofi-Aventis, Gilead, and CTI-Baxter.
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Table 1. JAK inhibitors tested in clinical trials in myelofibrosis

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<thead>
<tr>
<th>Agent</th>
<th>Other targets</th>
<th>Phase</th>
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<tr>
<td>Ruxolitinib</td>
<td>JAK1</td>
<td>III (approved)</td>
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<tr>
<td>Fedratinib (SAR302503)</td>
<td>FLT3, RET</td>
<td>III (withdrawn)</td>
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<tr>
<td>Pacritinib (SB1518)</td>
<td>FLT3</td>
<td>III</td>
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<tr>
<td>Momelotinib (CYT387)</td>
<td>JAK1, JNK1, TYK2, CDK2, RICJ2</td>
<td>III</td>
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<td>Lestaurtinib (CEP-701)</td>
<td>FLT3, TRKA</td>
<td>II (withdrawn)</td>
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<tr>
<td>AZD1480</td>
<td>JAK1, JAK3, FLT4, FGFR1, TRKA</td>
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<tr>
<td>Gandotinib (LY2784544)</td>
<td>-</td>
<td>I (withdrawn)</td>
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<tr>
<td>XL019</td>
<td>-</td>
<td>I (withdrawn)</td>
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<tr>
<td>NS-018</td>
<td>SRC, FLT3, ABL</td>
<td>I/II</td>
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<tr>
<td>BMS-911543</td>
<td>-</td>
<td>I/II (withdrawn)</td>
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Table 2. Drugs tested in combination with the JAK inhibitors in myelofibrosis

<table>
<thead>
<tr>
<th>Aimed at improving anemia</th>
<th>Aimed at a deeper effect</th>
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<tbody>
<tr>
<td>• ESA*</td>
<td>• Pegylated interferon</td>
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<td>• Danazol</td>
<td>• Histone deacetylase inhibitors</td>
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<td>• Hedgehog inhibitors</td>
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<td>• PI3K inhibitors</td>
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<tr>
<td></td>
<td>• HSP90 inhibitors</td>
</tr>
<tr>
<td></td>
<td>• PIM inhibitors</td>
</tr>
<tr>
<td></td>
<td>• pERK 1/2 inhibitors</td>
</tr>
<tr>
<td></td>
<td>• CDK 4/6 inhibitors</td>
</tr>
</tbody>
</table>

*Erythropoiesis-stimulating agents
### Table 3. Current prognostic models for myelofibrosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPSS</th>
<th>DIPSS</th>
<th>DIPSS-plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 yrs</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hb &lt; 10 g/dL</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Leukocytes &gt; 25 x 10⁹/L</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Blood blasts ≥ 1%</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt; 100 x 10⁹/L</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>RBC transfusion need</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Unfavorable karyotype: +8, -7/7q-, -5/5q-, i17q, 12p-, 11q23 rearr.</td>
<td>1 point each</td>
<td>1 point each (Hb: 2 points)</td>
<td>+</td>
</tr>
</tbody>
</table>

The patient’s DIPSS score (int-1: 1 point; int-2: 2 points; high: 3 points) plus one additional point for each of the following:
- Platelets < 100 x 10⁹/L
- Unfavorable karyotype
- Transfusion need

**IPSS:** International Prognostic Scoring System. Low risk: 0 points; intermediate-1 risk: 1 point; intermediate-2 risk: 2 points; high risk: 3-5 points

**DIPSS:** Dynamic IPSS. Low risk: 0 points; intermediate-1 risk: 1-2 points; intermediate-2 risk: 3-4 points; high risk: 5-6 points

**DIPSS-plus:** Low-risk: 0 points; intermediate-1 risk: 1 point; intermediate-2 risk: 2-3 points; high risk: 4-6 points
Table 4. New drugs other than the JAK inhibitors for myelofibrosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug class</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomalidomide</td>
<td>Immunomodulator</td>
<td>III (withdrawn)</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>Hypomethylating agent</td>
<td>II</td>
</tr>
<tr>
<td>Decitabine</td>
<td>Hypomethylating agent</td>
<td>I-II</td>
</tr>
<tr>
<td>Givinostat</td>
<td>Histone deacetylase inhibitor</td>
<td>II</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Histone deacetylase inhibitor</td>
<td>II</td>
</tr>
<tr>
<td>Everolimus</td>
<td>m-TOR inhibitor</td>
<td>II</td>
</tr>
<tr>
<td>Obatoclax mesylate</td>
<td>Bcl-2 inhibitor</td>
<td>II</td>
</tr>
<tr>
<td>AUY-922</td>
<td>HSP90 inhibitor</td>
<td>II</td>
</tr>
<tr>
<td>PF-04449913</td>
<td>Hedgehog inhibitor</td>
<td>II</td>
</tr>
<tr>
<td>PRM-151</td>
<td>Anti-fibrosis agent</td>
<td>II</td>
</tr>
<tr>
<td>GC-1008</td>
<td>Anti-fibrosis agent</td>
<td>I</td>
</tr>
<tr>
<td>GS-6624</td>
<td>Anti-fibrosis agent</td>
<td>I</td>
</tr>
<tr>
<td>Imetelstat</td>
<td>Telomerase inhibitor</td>
<td>I-II</td>
</tr>
<tr>
<td>IPI-926</td>
<td>Hedgehog inhibitor</td>
<td>I</td>
</tr>
<tr>
<td>LDE-225</td>
<td>Hedgehog inhibitor</td>
<td>I</td>
</tr>
<tr>
<td>BKM-120</td>
<td>PI3K/AKT inhibitor</td>
<td>I</td>
</tr>
<tr>
<td>MK-2206</td>
<td>PI3K/AKT inhibitor</td>
<td>Preclinical</td>
</tr>
<tr>
<td>ABT-737</td>
<td>BCL-X&lt;sub&gt;i&lt;/sub&gt; inhibitor</td>
<td>Preclinical</td>
</tr>
<tr>
<td>PU-H71</td>
<td>HSP90 inhibitor</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
Legends for the figures

Figure 1. Clinical manifestations of myelofibrosis.

Figure 2. Treatment algorithm for the anemia of myelofibrosis. Epo: erythropoietin; ESA: Erythropoiesis-stimulating agents; * <125 mU/mL

Figure 3. Treatment algorithm for patients with myelofibrosis.
Figure 2

Epo levels

- Inadequate*
  - ESA
    - Response at 3 months?
      - Yes: ESA
      - No: Immunomodulators

- Adequate
  - Danazol
    - Response at 6 months?
      - Yes: Danazol
      - No: Immunomodulators
How I treat myelofibrosis

Francisco Cervantes