World Journal of Hematology

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
doi:10.5315/wjh.v3.i3.85

World J Hematol 2014 August 6; 3(3): 85-92
ISSN 2218-6204 (online)

MINIREVIEWS

Myelofibrosis: Prognostication and cytoreductive treatment

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Received: November 2, 2013 Revised: February 8, 2014
Accepted: June 10, 2014
Published online: August 6, 2014

Abstract

Myeloproliferative neoplasms include three diseases: polycythemia vera, essential thrombocythemia and primary myelofibrosis (PMF), currently diagnosed according to the 2008 World Health Organization criteria. Patients with PMF may encounter many complications, and, among these, disease progression is the most severe. Concerning prognostication of Myelofibrosis (MF), the International Prognostic scoring system (IPSS) (International Prognostic Scoring System) model at diagnosis and the Dynamic IPSS (DIPSS) anytime during the course of the disease may be useful to define survival of MF patients. The IPSS and the DIPSS are based on age greater than 65 years, presence of constitutional symptoms, hemoglobin level less than 10 g/dL, leukocyte count greater than 25 × 10^9/L, and circulating blast cells 1% or greater. Cytogenetic profile and mutational analysis seem to be the next step to implement MF prognostication. Concerning treatments, hydroxyurea has been considered until now the drug of choice when an anti-myeloproliferative effect is needed, but recent data on JAK inhibitors demonstrated a significant effect of these drugs on splenomegaly and symptoms.

Key words: Myelofibrosis; Prognosis; JAK2; Ruxolitinib; Fedratinib; Momelotinib

Core tip: Myelofibrosis (MF) is a mutational/clinical-complex disease. Prognostication of MF is based on the International Prognostic scoring system (IPSS) model at diagnosis and on the Dynamic IPSS thereafter. Factors included in both models are: age > 65 years, constitutional symptoms, hemoglobin < 10 g/dL, leukocytes > 25 × 10^9/L, and circulating blast cells 1% or greater. Cytogenetic profile and mutational status help to better discriminate within each IPSS category. JAK inhibitors are new promising therapies with a molecular target, translating into a clinical benefit: spleen reduction MF-symptoms refief. Among JAK inhibitor, ruxolitinib has been approved for MF.

Maffioli M, Caramazza D, Mora B, Merli M, Passamonti F. Myelofibrosis: Prognostication and cytoreductive treatment. *World J Hematol* 2014; 3(3): 85-92 Available from: URL: http://www.wjgnet.com/2218-6204/full/v3/i3/85.htm DOI: http://dx.doi.org/10.5315/wjh.v3.i3.85

PROGNOSTICATION IN PMF

Among myeloproliferative neoplasms (MPN), primary myelofibrosis (PMF) has the most heterogeneous clinical presentation, including anemia, splenomegaly, leukocytosis or leukopenia, thrombocytosis or thrombocytopenia, and constitutional symptoms (fever, weight loss, night sweats). Available estimate of survival in MF fixes the median value at 6 years ranging from few months to many years[1]. Causes of death may be summarized into bone marrow failure (severe anemia, bleeding due to thrombocytopenia, and infections due to leukopenia) in 25%-30% of patients, leukemic transformation, named blast phase (BP), in 10%-20% of patients, cardiovascular

complications in 15%-20%, and portal hypertension in 10%.

Many factors affect survival in PMF such as advanced age[1,2], anemia[1], red blood cell transfusion need[1], leukopenia[3], leukocytosis[1], thrombocytopenia[1], peripheral blast count[1], systemic symptoms[1], hepatic myeloid metaplasia[4-22], decreased marrow cellularity with higher degree of fibrosis[23], higher degree of microvessel density[1], high number of circulating CD34-positive cells[1], cytogenetic abnormalities[1], the *JAK2* (V617F) mutation[1], some new mutation[1] and high level of some cytokines[24-30].

PROGNOSTIC FACTORS IN PMF

Cytogenetic abnormalities

Cytogenetic analysis has a role to identify an abnormal profile that provides evidence of clonality. Although most PMF patients' bone marrow aspirate results in a "dry tap", karyotype analysis can be performed on peripheral blood[29]. Among MPN, PMF shows the highest aberration rate with approximately 30% of patients carrying an abnormal karyotype at diagnosis[9]. The most frequent isolated abnormalities in PMF involve chromosome 1, 8, 9, 13 and 20[1]. Sole abnormalities of chromosome 7 were reported in 7% of PMF in a dedicated analysis and 7q- was the most frequent[1]. Concerning prognostic relevance of cytogenetic changes in PMF, recent studies have been consistently claiming an impact on survival[1]. Three studies, each comprising 202, 200 and 131 patients showed a favorable prognostic value for sole 20q- or sole 13q-[1]. A further study of 433 PMF patients refined a two-tired cytogenetic-risk stratification: unfavorable and favorable karyotype[1]. In detail, this study identified a high risk profile for cytogenetics when patients carry sole abnormalities of i(17q), -5/5q-, 12p-, 11q23 rearrangement, inv(3), sole +8 or sole -7/7q-, complex karyotype (three or more abnormalities), and a low-risk profile when patients carry normal diploid, or sole abnormalities not included in the high-risk profile. The respective 5-year survival rates were 8% and 51%. The presence of monosomal karyotype, which is defined as two or more autosomal monosomies or a single autosomal monosomy associated with at least one structural abnormality, identified a subset of patients with unfavorable karyotype associated with extremely poor overall and leukemia-free survival, as demonstrated in a study of 793 PMF patients[31].

Mutational profile

In PMF the prognostic role of the oncogenic mutations involving *MPL* and *JAK2* has been assessed, overall, not showing a significant effect on survival[1]. Concerning *JAK2* (V617F) allele burden, there is evidence that having a lower allele load implies a worse survival. In one study[7], survival was significantly reduced in the lower quartile compared with upper quartiles and *JAK2*^{wt} patients, mostly because of infections. In the second paper[27], Kaplan-Meier plots revealed significantly shortened overall and leukemia-free survival for the lower quartile allele burden group, mostly related to BP transformation. Intriguing results were obtained in PMF patients receiving allogeneic hematopoietic stem cell transplantation (HSCT)[32]. In 139 out of 162 patients with known *JAK2* (V617F) mutation status who received HSCT after reduced-intensity conditioning, overall survival was significantly reduced in patients harboring *JAK2*^{wt} compared with *JAK2* mutated patients. In addition, patients who cleared *JAK2* in the peripheral blood six months post-HSCT had a significant lower risk of relapse: this highlights the importance of complete molecular response in MF.

Mutations in the *EZH2* gene, acting through modifying chromatin structure and rendering genes involved in apoptosis inaccessible for transcription, have been found in roughly 6% of PMF[1]. Recently, in 370 PMF and 148 post-PV/ET MF genotyped for mutations of *EZH2* a total of 25 different mutations were detected. *EZH2*-mutated PMF patients had significantly higher leukocyte counts, blast cell counts, and larger spleens at diagnosis, and most of them (53%) were in the high-risk International Prognostic scoring system (IPSS) category. Leukemia-free survival (LFS) and overall survival (OS) were significantly reduced in *EZH2*-mutated PMF patients[1].

Mutations in *IDH* were detected in 4% of patients: 7 patients with mutations of *IDH2* (5 R140Q, 1 R140W and 1 R172G) and 5 of *IDH1* (3 R132S and 2 R132C)[24]. The estimate of survival disclosed that *IDH* mutations are associated with inferior OS and LFS. In addition, a more pronounced effect for the mutant *IDH* on OS and LFS was demonstrated in the context of the *JAK2* mutation.

After the identification of recurrent somatic mutations that involved different components of the RNA splicing machinery and other spliceosome-related genes in myelodysplastic syndromes, these mutations have been investigated in MPNs. A study on 155 MF identified *SF3B1* mutations in 6.5% of the patients: 4 (40%) K700E, 4 (40%) K666T/N/M, 1 (10%) H662D and 1 (10%) N626S and failed to demonstrate any prognostic relevance[11]. In a subsequent study on 187 patients, 17% harbored *SRSF2* monoallelic mutations affecting residue P95[1]. Significant associations were demonstrated between *SRSF2* mutations and advanced age, *IDH* mutations, and higher DIPSS-plus risk category. Finally, *SRSF2* mutations were associated with shortened OS and LFS.

Very recently, a total of 879 MF patients were studied to determine the individual and combinatorial prognostic relevance of somatic mutations in *ASXL1, SRSF2, EZH2, TET2, DNMT3A, CBL, IDH1, IDH2, MPL* and *JAK2* in patients with MF[1]. Analysis was performed in 483 European patients and the seminal observations were validated in 396 patients from Mayo Clinic, Rochester, United States. Of these, *ASXL1, SRSF2*, and *EZH2* mutations inter-independently predicted shortened survival. However, only *ASXL1* mutations remained

significant in the context of the International Prognostic Scoring System (IPSS) with a hazard ratio (HR) of 2.02. These observations were validated in the Mayo Clinic cohort, where investigators found that *ASXL1, SRSF2* and *EZH2* mutations were independently associated with poor survival, but only *ASXL1* mutations held prognostic relevance independently from the Dynamic IPSS (DIPSS)-plus model, with a HR of 1.4. In the European cohort, LFS was negatively affected by *IDH1/2, SRSF2* and *ASXL1* mutations and in the Mayo cohort by *IDH1* and *SRSF2* mutations. In conclusion, the study identified *ASXL1* mutations as the most relevant to be included in the patient's evaluation besides the IPSS models. *ASXL1* mutations are however present at low frequency (less than 20%) in lower risk IPSS categories.

However, the most recent discovery in MF is the occurrence of *CALR* (calreticulin) mutation in patients with MPN without *JAK2* or *MPL* mutation[10,16] and in familial MPN[12]. In MF a clear association with survival has been documented[26].

Proinflammatory cytokines

The abnormal cytokine profile in PMF means that PMF is, at least in part, an inflammatory disease. Cytokines contribute to clinical phenotype, bone marrow fibrosis, angiogenesis, extramedullary hematopoiesis and constitutional symptoms. The interest on cytokines in PMF has recently arisen as JAK inhibitors may quickly reduce several proinflammatory cytokines[1]. Mayo Clinic investigators found that among 30 cytokines tested in a cohort of 90 treatment-naive patients with PMF, high levels of IL-8, IL-2R, IL-12, IL-15 correlate with inferior survival independently from conventional risk stratification[31]. In detail, the presence of 3-fold increased levels of one or both IL-8 and IL-2R may predict worse survival. C-reactive protein (CRP) is a simple marker of systemic inflammation mediated by cytokines, mainly IL-6, and it has been found in MF as well as in ET and PV at higher level than in healthy controls. In PV and ET, high-sensitivity CRP (hsCRP) correlated with a higher risk of vascular complications. In MF hsCRP seems to be associated with a higher incidence of BP and this seems independent from models used to predict survival in MF. To explain this association investigators even speculated on a mutagenic role of chronic oxidative stress on the stem cell, but this seems premature as, for example, new JAK inhibitors, which are able to reduce CRP expression, don't affect leukemic evolution.

Plasma immunoglobulin free light chain

Plasma immunoglobulin FLC might be considered as a surrogate marker of host immune response. free light chain (FLC) (κ or λ) values above the upper limit of normal have been documented in 33% of 240 patients with PMF[18]. Increases in FLC were significantly associated with increased creatinine and advanced age in PMF. In multivariable analysis, increased FLC predicted shortened survival independently from age, creatinine, and other conventional risk factors. No correlations were seen with LFS, karyotype, or *JAK2, MPL*, or *IDH* mutations. In patients with PMF who were studied by cytokine profiling, the prognostic value of an increased FLC level was independent of that from circulating IL-2R or IL-8 levels.

Red blood cell transfusion dependency

Criteria to define red blood cell (RBC) transfusion dependency in PMF have been published[5], and recently updated[6]. Experts considered a volume of 2 units of RBC/month over three months to be the most appropriate observational interval and RBC-transfusion frequency to define a person as RBC-transfusion-dependent. In general, the cutoff level of hemoglobin to define the need of RBC transfusion is 8.5 g/dL. The prognostic impact of RBC transfusion need was examined in 254 consecutive patients, of whom 24% required RBC transfusions at diagnosis and 9% became RBC transfusion dependent during the first year after diagnosis[1]. RBC transfusion need clearly separated two groups with different survivals: 35 mo (transfused from diagnosis), 25 mo (transfused within 1 year), and 117 months (not transfused). RBC transfusion need had an IPSS-independent prognostic power downgrading or upgrading prognosis within specific IPSS categories. This result was confirmed by a study on 288 consecutive patients with PMF[4].

Only 5% of transfusion-independent patients have iron overload as compared to 72% of transfusion-dependent patients[1]. Iron homeostasis is potentially an intriguing pathway in MF. Prognostic interdependence among serum hepcidin (key regulator of iron homeostasis), serum ferritin, hemoglobin of < 10 g/dL, and RBC transfusion requirement has been described although only increased hepcidin and ferritin levels had independent prognostic value for survival in MF. Homeostatic control of hepcidin by iron is preserved in MF, as demonstrated by the strong positive correlation between hepcidin and ferritin levels. In addition, the absence of correlation between hepcidin and circulating inflammatory cytokine levels indicates that hepcidin levels are mainly controlled by iron loading or advanced disease and not by inflammatory signal. The role of iron chelation in MF has not been yet investigated, but some reports showed improvement in term of iron deposits and hemoglobin level[15].

Prognostic models for survival at diagnosis of PMF

In the last years many prognostic models have been developed in PMF. The most used in the past was the Lille score[3], recently replaced by the IPSS[1].

IPSS score

The IPSS was defined through the collaboration of seven centers under the auspices of the IWG-MRT in 2009[1]. After a systematic individual case review, the database included 1054 patients with PMF defined accord-

Table 1 Score values for international prognostic scoring system and dynamic international prognostic scoring system

Parameter	Scores	
	IPSS	DIPSS
Age > 65 yr	1	1
Hemoglobin < 10 g/dL	1	2
Leukocyte count > 25 × 10^9/L	1	1
Blast cells ⩾ 1%	1	1
Constitutional symptoms	1	1

IPSS: Score 0 for low risk, score 1 for intermediate risk-1, score 2 for intermediate risk-2, score ⩾ 3 for high risk; DIPSS: Score 0 for low risk, score 1-2 for intermediate risk-1, score 3-4 for intermediate risk-2, score 5-6 for high risk.

Table 2 Score values dynamic international prognostic scoring system-plus

Parameter	Score value
DIPSS intermediate-1	1
DIPSS intermediate-2	2
DIPSS high risk	3
Unfavorable cytogenetics	1
Red blood cell need	1
Platelet < 100 ×10^9/L	1

DIPSS-plus: Score 0 for low risk, score 1 for intermediate risk-1, score 2-3 for intermediate risk-2, score 4-6 for high risk; DIPSS: Dynamic International Prognostic scoring system-plus.

ing to the WHO classification system, excluding post-PV and post-ET MF and prefibrotic PMF. This is the largest prognostic study ever performed in PMF. Median survival was 69 mo. Multivariate analysis of parameters obtained at disease diagnosis identified age greater than 65 years, presence of constitutional symptoms, hemoglobin level less than 10 g/dL, leukocyte count greater than 25 × 10^9/L, and circulating blast cells 1% or greater as predictors of shortened survival. Based on the presence of 0 (low risk), 1 (intermediate risk-1), 2 (intermediate risk-2) or greater than or equal to 3 (high risk) of these variables, four risk groups with no overlapping in their survival curves were generated (Table 1). The four risk categories were well balanced: 22% of patients fell into the low risk category, 29% in the intermediate risk-1, 28% in the intermediate risk-2 and 21% in the high risk. Median survivals were 135 mo for low risk patients, 95 mo for intermediate-1 patients, 48 mo for intermediate-2 patients, and 27 mo for high risk patients.

Among these patients, 409 patients had available cytogenetic analysis at diagnosis: an abnormal karyotype implied a shorter survival primarily restricted to patients in the intermediate-1 and -2 risk categories. Concerning the *JAK2* (V617F) mutation, no association was observed between *JAK2* status and prognostic score or survival.

Dynamic models for survival in PMF

The progressive nature of PMF generated interest in defining new so-called dynamic models, such as the dynamic-IPSS (DIPSS) and the most recent DIPSS-Plus. In a non time-dependent analysis (models at diagnosis), patients are assigned to a risk group on the basis of the assessment of risk factors at diagnosis, and are followed in the same category irrespective of the acquisition of other risk factors during disease course. According to a dynamic model, patients contribute to the estimate of survival in a category only as long as they do not acquire further risk factors, then they shift to a higher category according to their new score.

DIPSS model

The DIPSS was developed in 525 PMF patients regularly followed[1]. DIPSS risk factors are age greater than 65 years, presence of constitutional symptoms, hemoglobin level less than 10 g/dL, leukocyte count greater than 25 × 10^9/L, and circulating blast cells 1% or greater. The scoring system of DIPSS is different from IPSS (Table 1). The resulting DIPSS risk categories are low (score 0), intermediate-1 (score 1 or 2), intermediate-2 (score 3 or 4) and high (score 5 or 6). Median survival was not reached in low risk patients; it was 14.2 years in intermediate-1, 4 years in intermediate-2, and 1.5 years in high risk. From a practical point of view, anytime a decision has to be made on the basis of an updated prognostic status, the parameters of the DIPSS models will be checked and corresponding values will be assigned. The sum of the values will allow allocating the patient into a risk category (low, intermediate-1, intermediate-2, high) and cumulative survival can be estimated. It is obvious that the corresponding cumulative probability of survival at each time point of the follow-up should be read considering the time elapsed since diagnosis. This estimate remains applicable thereafter until the patient changes risk category. The DIPPS model was also able to predict also the evolution to BP[20].

Very recently Scott *et al*[23] found that DIPSS categories at the time of HSCT predict post-transplant outcome in 170 patients with PMF (related donor, 86; unrelated donor, 84). After a median follow-up of 5.9 years, the median survivals have not been reached for DIPSS low and intermediate-1 risk groups, and were 7 and 2.5 years for intermediate-2 and high-risk patients, respectively.

DIPSS-plus model

This model was produced in 793 patients with PMF of which 428 were referred within and 365 after their first year of diagnosis[1]. This composite model included as worse prognostic factors the unfavorable cytogenetics as previously grouped (complex, sole or two including +8, -7/7q-, i(17q), inv (3), -5/5q-, 12p-, 11q23 rearrangements), RBC transfusion need, platelet count lower than 100 × 10^9/L, and DIPSS categories. According to the model, 1 point each was assigned to DIPSS intermediate-1 risk, unfavorable karyotype, platelets lower than 100 × 10^9/L, and RBC transfusion need, while DIPSS intermediate-2 and high risk were assigned 2 and 3

points, respectively (Table 2). On the basis of this scoring system, four categories were generated: low risk (0 adverse points; median survival, 185 mo), intermediate-1 risk (1 adverse point; median survival, 78 mo), intermediate-2 risk (2-3 adverse points; median survival, 35 mo), and high risk (4-6 adverse points; median survival, 16 mo). It's interesting to note that DIPSS-plus investigators found a proportion of patients in each DIPSS risk category with RBC transfusion need, unfavorable karyotype, and thrombocytopenia, namely 0% (RBC transfusion need), 7% (unfavorable karyotype), and 7% (thrombocytopenia) in low risk patients, 13%, 12%, and 18% in intermediate-1 risk patients, 56%, 17%, and 32% in intermediate-2 risk patients; and 69%, 23%, and 47% in high risk patients, respectively. This sheds light into the possibility of better stratifying patients with lower risk categories.

ANTI-MYELOPROLIFERATIVE AGENTS

The ELN guidelines recommended to use hydroxyurea (HU) as drug of choice when an anti-myeloproliferative effect is needed in MPNs[1]. However, data available on HU are scant. The most complete study on HU in MF evaluated retrospectively 40 patients[1]. Reasons for treatment were constitutional symptoms (55%), symptomatic splenomegaly (45%), thrombocytosis (40%), leukocytosis (28%), pruritus (10%), and bone pain (8%). Responses on different symptoms/clinical findings were as follows: bone pain in 100%, constitutional symptoms in 82%, pruritus in 50%, splenomegaly in 40%, and anemia in 12.5%. According to the IWG-MRT criteria[1], clinical improvement was achieved in 16 patients (40%). Despite the high rate, the median duration of response was 13.2 mo. Worsening of anemia or appearance of pancytopenia were observed in half of the patients.

JAK inhibitors

In the last few years several medicines with anti JAK properties, named JAK inhibitors (JAKi) have been studied. Among these, ruxolitinib is the only approved in many States and available for clinical practice. Other compounds are nowadays under phase 3 investigation (fedratinib, momelotinib, pacritinib), while others are being tested in phase 1-2 studies (www.clinicaltrials.gov). For the practical purpose of this review only ruxolitinib, fedratinib and momelotinib will be discussed in detail as only data published as a full paper will be taken into account.

Ruxolitinib

A phase Ⅰ/Ⅱ trial with ruxolitinib (oral drug) was conducted in 152 patients with PMF or post-PV/post-ET MF. Eligible subjects were therapy-requiring patients, refractory, relapsed, intolerant to previous therapy, or patients with intermediate or high-risk Lille score, if at diagnosis. Main exclusion criteria were thrombocytopenia (platelets < 100×10^9/L) and neutropenia. Applying IWG-MRT criteria[1], 44% of patients obtained a clinical improvement of spleen size (≥ 50% reduction from baseline, measured by palpation) at 3 mo and responses were maintained at 12 mo in more than 70% of patients. The majority of patients had more than 50% improvement in constitutional symptoms mostly due to the activity against pro-inflammatory cytokines[1]. The reduction of the *JAK2*(V617F) allele burden was modest. This study was mainly conducted at MD Anderson Cancer Center (MDACC), Houston, and at Mayo Clinic, Rochester. Two comparisons of outcomes from this phase Ⅰ/Ⅱ trial with historical controls have been performed separately in the two centers to test the effect of ruxolitinib on survival. Mayo Clinic investigators compared 51 patients who received ruxolitinib at Mayo Clinic with 410 patients from the Institutional database not showing any difference in term of survival[28]. The second study compared 107 patients treated with ruxolitinib at MDACC with 310 patients (from three different centers) matched for the phase 1-2 study entry criteria, as controls[1]. A survival benefit for patients treated with ruxolitinib was demonstrated. In addition, the study demonstrated that patients treated with ruxolitinib who obtained a reduction of spleen size greater than 50% have a significantly better survival than those who did not[1].

Two prospective randomized trials with ruxolitinib have been published: COMFORT-1 (155 ruxolitinib *vs* 151 placebo)[1] and COMFORT-2 (146 ruxolitinib vs. 73 best available therapy, BAT)[1]. In COMFORT-1, the primary endpoint (reduction of spleen volume by MRI equal to or greater than 35%) at week 24 was reached in 42% of patients in the ruxolitinib arm and in 1% of those in the placebo arm. At week 24, 46% of patients receiving ruxolitinib and 5% of those receiving placebo experienced symptom alleviation by at least 50%, as measured by the modified Myelofibrosis Symptom Assessment Form (MF-SAF)[14]. Patients treated with ruxolitinib experienced relief of abdominal discomfort, early satiety, night sweats, itching, musculoskeletal pain[1]. In the COMFORT-2 trial the primary endpoint (the same as the COMFORT-1 study but evaluated at week 48) was reached in 28% of patients treated with ruxolitinib and in 0% of those receiving BAT; at week 24 the figures were 32% and 0%, respectively. Mean improvements from baseline in FACT-LymS (Functional Assessment of Cancer Therapy-Lymphoma System) were greater in the ruxolitinib arm.

Recently, the long-term (median time, 2 years) data from the COMFORT-1 trial has been published: 100 of 155 patients randomized to ruxolitinib were still receiving treatment[33]. Mean spleen volume reductions in the ruxolitinib group were 32% at week 24 and 35% at week 96; improvements in quality of life measures were also maintained. Improved survival was observed for ruxolitinib (n = 27 deaths) *vs* placebo (n = 41 deaths) with a hazard ratio of 0.58 (95%CI: 0.36-0.95). Dose-dependent anemia and thrombocytopenia were the most common adverse events in the ruxolitinib group, but these

events rarely led to discontinuation. The incidence of new-onset grade 3 or 4 anemia (29% and 11%, respectively) and thrombocytopenia (9% and 3%, respectively) reported in the first 6 mo of therapy decreased over time to less than 5% for anemia and less than 2% for thrombocytopenia. Mean hemoglobin values reached a nadir of 10%-12% below baseline between weeks 8 and 12 and stabilized over time to a new steady-state slightly below baseline by week 24, and then remained stable throughout the remaining follow-up. In the first 6 mo of treatment, the most common non-hematologic adverse events that occurred more frequently in the ruxolitinib group compared with the placebo group were ecchymosis, headache and dizziness. Under ruxolitinib the rate of non-hematologic adverse events reduced over time. Two patients originally randomized to receive ruxolitinib developed BP at the time of the primary analysis[1] and no further cases were reported in this group.

COMFORT-2 trialists updated the 3 year-follow with 45% (66 of 146) of those originally randomized to ruxolitinib remaining on treatment. The 3-year probability to maintain spleen response (greater than 35%, by MRI) was 50% among patients achieving such degree of response. Ruxolitinib continues to be well tolerated. Anemia and thrombocytopenia were the main toxicities, but they were generally manageable, improved over time, and rarely led to treatment discontinuation (1% and 3.6% of patients, respectively). Other adverse events of special interest included leukopenia, bleeding, infections, thromboembolic events, elevated transaminase levels, increased systolic blood pressure, weight gain. The rate of these events generally decreased with longer exposure to ruxolitinib treatment, with the highest rates occurring within the first 6 mo of treatment. Among these events, infections occurred in 50% of patients between weeks 0-24 and included bronchitis, gastroenteritis, nasopharyngitis, urinary tract infections. The rate of infections becomes 25% in weeks 144-168. Over the entire course of the study, 2 patients (1.4%) in the ruxolitinib arm had tuberculosis. No single non-hematologic adverse event led to definitive ruxolitinib discontinuation in more than one patient. Finally, patients randomized to ruxolitinib showed longer overall survival than those randomized to BAT (HR = 0.48, 95%CI: 0.28-0.85).

Both COMFORTs trial included patients with placebo or BAT who crossed to ruxolitinib: this makes impossible the evaluation of the net effect of ruxolitinib over comparators in the long term. Very recently, a comparison of survival from diagnosis of the DIPSS cohort (350 PMF, selection criteria, patients who become intermediate-2 and high risk IPSS, blast cell count lower than 10%) and the COMFORT-2 cohort (100 patients, intermediate-2 and high risk IPSS, blast cell count lower than 10%, selection criteria, PMF) has been published. This demonstrated an advantage in term of survival using ruxolitinib (COMFORT-2) *vs* standard therapy (DIPSS)[21].

Taken together the COMFORT trials showed that ruxolitinib, a drug with a good safety profile, improves two clinical needs of patients: splenomegaly and MF-related symptoms. However, reactivation of infections such as tuberculosis or viral hepatitis has been reported in very few case reports[1] and this underlines the need for a careful observation of patients during follow-up. *In vitro* data[8] demonstrated that ruxolitinib significantly affects dendritic cell differentiation and function leading to impaired T-cell activation[13], potentially resulting in increased infection rates in ruxolitinib-treated patients. Though requiring adequante monitoring for these potential side effects, data on survival advantage are really interesting and place this drug as a new potential first line therapy in MF patients at higher risk.

Fedratinib, SAR302503

In a phase Ⅰ-Ⅱ trial, fedratinib was administered orally once a day to 59 patients with intermediate and high-risk MF[1]. By six and 12 cycles of treatment, 39% and 47% of patients, respectively, had achieved a spleen response per IWG-MRT criteria. The majority of patients with leukocytosis or thrombocytosis at baseline achieved normalization of blood counts after six (57% and 90%, respectively) and 12 (56% and 88%, respectively) cycles. Beside the effect on splenomegaly, the majority of patients with constitutional symptoms, fatigue, pruritus had a durable resolution. Grade 3 to 4 hematologic adverse events included anemia (occurring in 35% of 37 patients who were not RBC transfusion dependent at baseline), thrombocytopenia (24%) and neutropenia (10%). At doses ranging between 240 mg and 520 mg, two of five RBC transfusion-independent patients became RBC transfusion-dependent and two of nine had grade 3/4 thrombocytopenia. The main non-hematologic adverse events included all grades nausea (69%), diarrhea (64%) vomiting (58%), all self-limited and controlled by symptomatic treatments. Asymptomatic increase of lipase, AST, ALT, and creatinine have been reported in roughly one quarter of patients. A randomized, blinded, placebo-controlled study of fedratinib (dose 400 mg or 500 mg daily), named JAKARTA, in patients with intermediate-2 or high risk MF is ongoing with the objective to evaluate the reduction of spleen volume by MRI equal to or greater than 35%. Unfortunately, despite this pivotal study met the primary endpoint in both dose groups, cases consistent with Wernicke's encephalopathy have been reported in patients participating in fedratinib trials. Following a thorough risk-benefit analysis, the risk to patient safety was considered to outweigh the benefit that fedratinib would bring to patients. All clinical trials involving fedratinib have been halted, and fedratinib treatment discontinued in patients enrolled in ongoing trials.

Momelotinib, CYT387

Momelotinib was studied in a phase 1/2 trial in patients with high or intermediate risk MF[17]. Pre-planned safety and efficacy analysis has been completed for the initial

60 patients. In the dose-escalation phase, the maximum-tolerated dose was 300 mg/d based on reversible grade 3 headache and asymptomatic hyperlipasemia. Twenty-one and 18 additional patients were accrued at two biologically effective doses, 300 mg/d and 150 mg/d, respectively. Anemia and spleen responses, per IWG-MRT criteria, were 59% and 48%, respectively. Among 33 patients who were RBC-transfused in the month prior to study entry, 70% achieved a minimum 12-wk period without transfusions. Most patients experienced constitutional symptoms improvement. Grade 3/4 adverse reactions included thrombocytopenia (32%), hyperlipasemia (5%), elevated liver transaminases (3%) and headache (3%). New-onset treatment-related peripheral neuropathy was observed in 22% of patients (sensory symptoms, grade 1). A phase 3 study to determine the efficacy of momelotinib *vs* ruxolitinib in MF patients naive of JAKi is ongoing.

CONCLUSION

Concerning prognostication of MF, the IPSS model at diagnosis and the DIPSS anytime during the course of the disease may be useful to define survival of MF patients. The IPSS and the DIPSS are based on age greater than 65 years, presence of constitutional symptoms, hemoglobin level less than 10 g/dL, leukocyte count greater than 25×10^9/L, and circulating blast cells 1% or greater. Cytogenetic profile and mutational analysis seem to be the next step to implement MF prognostication. Taking together all available clinical data on MF, one may conclude that JAKi give a benefit to patients with MF, by reducing spleen size of about 50% in approximately 30%-40% of patients and by abolishing symptoms in the vast majority of patients. However, effect on these disease manifestations should be balanced with the safety profile[19]. Anemia and thrombocytopenia are on-target toxicities expected with all JAKi. Infections should be monitored with ruxolitinib, drug with the longest time of observation, but might be expected with all JAKi. Other toxicities may involve non-JAK2 targets, as in case of gastrointestinal events during therapy with fedratinib or in the case of neurological toxicity for momelotinib.

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P- Reviewer: Ren G, Ribera JM **S- Editor**: Qi Y **L- Editor**: A
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