Disease characteristics in Belgian myelofibrosis patients and management guidelines anno 2013

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Diagnostic and management guidelines for myelofibrosis patients are presented in this paper. As a consequence of the rapid evolution and progress in this domain over the last years, the need was felt by the BHS MPN subcommittee to update these guidelines for our country. The different prognostic scores in myelofibrosis, the diagnostic tools and treatment options with the focus on new possibilities are discussed.
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Introduction

Myelofibrosis (MF) is the Philadelphia-chromosome negative myeloproliferative neoplasm (MPN) with the lowest incidence but the worst prognosis. MF can be primary (PMF) or can develop from an earlier existing PV (PPV-MF) or ET (PET-MF). MF is a progressive, chronic myeloid neoplasm resulting in intramedullary fibrosis, progressive cytopenia, splenomegaly and debilitating constitutional symptoms. The estimated incidence of PMF is 0.5 - 1.5 per 100 000 with a median age of 67 years.[1]

The diagnosis of PMF is based on the 2008 World Health Organization (WHO) criteria.[2] The diagnosis of PPV-MF and PET-MF should be made according to IWG-MRT criteria.[3] Leukemic transformation should be called blast-phase MF.[4] These criteria are described in *Table 1*. The identification of prefibrotic PMF is still a matter of debate and will not be discussed in this paper. Over the last years, different prognostic markers have been identified, leading to three consecutive prognostic scores in three years time: the International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS) and the DIPSS plus.[5-7] These scores have been of high value for the development of a novel risk-adjusted therapy in MF.

The description of the JAK2 V617F mutation in 2005, present in about 60% of MF patients, profoundly changed the diagnostic and therapeutic landscape of MF. It revealed the crucial role played by the JAK/STAT pathway in the pathogenesis of MPN and opened the way for the development of small ATP-competitive molecules, the JAK tyrosine kinase inhibitors.

Moreover, other progresses were accomplished in recent years: improvement of reduced intensity conditioning (RIC) regimens for allogeneic hematopoietic stem cell transplantation, better supportive care measures and the development of new molecules explored in different clinical trials.

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Table 1. Diagnostic criteria of myelofibrosis

Primary Myelofibrosis (PMF)[2]
Diagnosis requires meeting all three major criteria and two minor criteria
Major criteria • Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterised by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular-phase disease) • Not meeting WHO criteria for polycythemia vera, BCR-ABL1–positive chronic myelogenous leukaemia, myelodysplastic syndrome, or other myeloid disorders • Demonstration of JAK2 V617F or other clonal marker (e.g., MPLW515K/L), or, in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukaemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies
Minor criteria • Leukoerythroblastosis • Increase in serum lactate dehydrogenase level • Anaemia • Palpable splenomegaly
Criteria for post-polycythemia vera myelofibrosis[3]
Required criteria: 1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria 2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)
Additional criteria (two are required): 1. Anaemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. A leukoerythroblastic peripheral blood picture. Increasing splenomegaly defined as either an increase in palpable splenomegaly of >= 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly 3. Development of >= 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)
Criteria for post-essential thrombocythemia myelofibrosis[3]
Required criteria: 1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria 2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)
Additional criteria (two are required): 1. Anaemia and a > 2 g/dl decrease from baseline haemoglobin level 2. A leukoerythroblastic peripheral blood picture 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of >= 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly 4. Increased LDH (above reference level) 5. Development of >= 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)
Blast-phase MF:
Documentation of a previous diagnosis of PMF, post-PV MF or post-ET MF More than 20 % of blasts in the blood or the bone marrow

As such, MF has become an intense and attractive field for research and development. As a consequence of these recent evolutions, it became clear that there was a need for therapeutic guidelines concerning the treatment of MF in Belgium, which is the aim of this paper. In conjunction, we took advantage of a scientific survey to describe MF disease characteristics in our country. This survey was held in Belgium with the collaboration of eighteen major Haematology centres, with the purpose to study specific disease parameters in all MF patients. In total 250 MF patients were enlisted. All patients were seen in 2011 at one of the collaborating

Table 2. Prognostic scoring systems in myelofibrosis[1]

Table 2a. The recent international risk scoring systems in MF.

Prognostic score	Age (years)	Hb (g/dl)	WBC (10^9/L))	Blast PB	Constitutional symptoms	Blood Platelets	Karyotype*	Transfusion Need
IPSS[5]	> 65 1 point	< 10 1 point	> 25 1 point	≥ 1% 1 point	+ 1 point	NC	NC	NC
DIPSS[6]	> 65 1 point	< 10 2 points	> 25 1 point	≥ 1% 1 point	+ 1 point	NC	NC	NC
DIPPS Plus[7]	DIPSS low risk: 0 point DIPSS intermediate-1: 1 point DIPSS intermediate-2: 2 points DIPSS high risk: 3 points					< 100 x 10^9/L 1 point	Unfavourable 1 point	dependent 1 point

**Unfavourable karyotype defined as complex or either a sole or two abnormalities including +8, 7/7q-, i(17q), 5/5q-, 12p, inv(3) or 11q23 rearrangement*
PB: peripheral blood, NC: not counted

Table 2b. Risk groups in MF and prognostic value of the scoring systems

Risk scoring system	risk group	score	median survival (months) (95% CI)
IPSS[5]	Low risk Intermediate-1 Intermediate-2 High risk	0 1 2 > 2	135 (117-181) 95 (79-114) 48 (43-59) 27 (23-31)
DIPSS[6]	Low risk Intermediate-1 Intermediate-2 High risk	0 1-2 3-4 5-6	NR 170 48 18
DIPPS Plus[7]	Low risk Intermediate-1 Intermediate-2 High risk	0 1 2-3 4-6	180 80 35 16

NR: not reached

hospitals and the descriptive data represent one specific time point during that year. Analysis was done on aggregated data and no data of the evolution of the patients were collected.

Prognostic scores

Therapeutic decisions in MF are based on patient's symptoms and prognosis. The accurate assessment of patient prognosis is particularly important when considering allogeneic stem cell transplantation. In 2009, the International Working Group for MF Research and Treatment (IWG-MRT) issued a scoring system (IPSS) based on 1,054 PMF patients and identified five key predictive parameters (age, haemoglobin level, white blood cell count, percentage of blasts and constitutional symptoms) (*Table 2*).[5]

To allow prediction of prognosis at any time during the course of PMF, a dynamic IPSS score (DIPSS) has been developed, taking into account that changes in the disease over time with acquisition of additional risk factors not present at diagnosis, can affect survival.[6] The same five risk factors as in the IPSS are used in this model but acquisition of anaemia was assigned a higher score (*Table 2*).

Erythrocyte transfusion dependence, thrombocytopenia and unfavourable karyotype were added in the DIPSS plus scoring system (*Table 2*).[7]

In the Belgian MF survey, 10% of the MF patients were low risk according to the DIPSS score, 49% were intermediate-1, 34% intermediate-2 and 8% high risk.

Recommendations

- *The prognostic risk scores in myelofibrosis, with a preference for the DIPSS or the DIPSS plus score, make an optimal risk-adjusted treatment possible. Karyotyping should be obtained for every patient and can usually be performed on peripheral blood in myelofibrosis because of the high number of circulating progenitor cells (Evidence level II, grade B).*
- *The IPSS score is valid at diagnosis, while the DIPSS and DIPSS plus scores can be used at any time during the disease (Evidence level II, grade B).*

Curative treatment: allogeneic hematopoietic stem cell transplantation

Allogeneic stem cell transplantation is the only curative option for MF and is the only treatment able to affect the long-term evolution of the disease. However, the selection of adequate candidates for stem cell transplantation is essential to reduce the morbidity and mortality induced by this procedure. An extended risk-benefit analysis should always be performed.

The European LeukaemiaNet (ELN) recommends that it is reasonable to justify the risk of allogeneic stem cell-related complications in transplant-eligible MF patients whose median survival is expected to be less than five years.[8] It is thus generally accepted that only intermediate-2 and high risk MF patients should be considered for allogeneic stem cell transplantation, as well as blast-phase MF. The eligibility for transplantation should be otherwise based on age, co-morbidities and patient's preference.[9] Since advanced disease is associated with poor survival, it is important to avoid long delay in fit patients showing clear signs of progression.[10]

Age is an important factor for the selection of suitable transplant candidates. In the Belgian survey, out of 250 MF patients, 97 (39%) were ≤65 years old and 153 (61%) >65 years. Of the patients ≤ 65 years old, 25 (26%) were low risk IPSS, 34 (35%) intermediate-1, 26 (27%) intermediate-2 and twelve (12%) high risk. This means that only 15,2% of all patients were transplant candidates. However, age above 65 is not a strict exclusion criterion for transplantation. Samuelson et al. described a three year progression free survival of 40 % in a patient population aged 60-78 years, with twelve out of 30 patients being above 65.[11]

Pre-transplantation splenectomy generally leads to earlier engraftment. However, this procedure is associated with clear morbidity and mortality, does not influence overall survival or graft failure, and could be associated with a greater risk of relapse.[12] Therefore, splenectomy cannot be systematically recommended before transplantation.

Myeloablative conditioning (MAC) transplantation is able to cure MF but carries significant mortality and morbidity.[1] MAC should be offered to young and fit patients or to blast-phase MF. Recently, several reports described interesting results with reduced intensity conditioning (RIC) transplantation.[1,12] This procedure extends the indications of transplantation in MF. There is no direct comparison between MAC and RIC, neither between the different conditioning regimens used in RIC. Most of the RIC regimens contain fludarabine and busulfan.

One study suggests that JAK2 V617F positive patients have better survival than JAK2 V617F negative patients after RIC.[13] In addition, it is possible in JAK2 V617F positive patients to monitor the allele burden after transplantation. Time to reach JAK2 V617F negativity can take up to six months after RIC.[13] As such, monitoring should be started at three months after transplantation. Patients positive for JAK2 V617F at six months post transplant have a greater chance of relapse compared with patients who cleared their JAK2 V617F allele burden (35% versus 5%).[13] However, several patients remained positive for JAK2 V617F after transplant without relapsing.[14] Therefore minimal residual disease should not be treated, unless there is evidence of molecular progression. Donor lymphocyte infusions may be useful as it has been shown that DLI induces a graft-versus-myelofibrosis-effect.[15]

The role of JAK2 inhibitors in the pre-transplantation setting is currently under investigation. They could improve the outcome of transplanted MF patients because of the reduction of the spleen size and because of the improvement of performance status and general condition pre-transplantation. However, several questions remain unanswered, such as the effect of cytokine modulation on graft-versus-host disease (GvHD), the timing of JAK2 inhibitor cessation or their effect on early engraftment. Therefore, participation in trials testing the role of JAK inhibition before transplant is encouraged.

Figure 1. Distribution of patients with constitutional symptoms according to DIPSS risk category

DIPSS risk category (n =250)	Constitutional symptom(s) present (n=86)
Low risk (10%) 25	0
Intermediate-1 (49%) 122	33 (27%)
Intermediate-2 (33%) 83	38 (45%)
High risk (8%) 20	15 (79%)

As the rate of graft failure is rather high in allogeneic transplanted MF patients, an autologous stem cell collection could be performed before starting conditioning. As MF patients have spontaneously elevated levels of circulating $CD34^+$ cells, no stimulation with G-CSF is needed before apheresis. In case of graft failure accompanied with life-threatening infections, these easily available stem cells can be infused.

Recommendations

- *Only intermediate-2 or high risk myelofibrosis and blast phase patients should be considered for allogeneic stem cell transplantation (Evidence level II, grade B).*
- *Blast-phase myelofibrosis or fit patients below 45 years of age should be considered for myeloablative conditioning. Other patients can be transplanted with reduced intensity conditioning regimens (Evidence level III, grade C).*
- *Pre-transplant splenectomy is not routinely recommended (Evidence level III, grade C).*
- *JAK2 V617F monitoring by polymerase chain reaction on peripheral blood granulocytes is advised in mutated myelofibrosis patients, starting three months post transplantation (Evidence level II, grade B).*
- *Myelofibrosis patients with molecular progression after transplant or in haematological relapse should be considered for donor lymphocyte infusions (Evidence level II, grade B).*

Watch-and-wait or symptomatic treatment

No treatment other than allogeneic stem cell transplantation is able to modify the biological course of the disease, to decrease the probability for evolution to blast phase or to prolong survival. This could change in the future, as illustrated by the survival benefit observed with ruxolitinib, the first-in-class JAK inhibitor, that has recently been confirmed by analysing the two-year follow up data of the COMFORT-I and -II trials.[16-20]

Low or intermediate-1 risk patients with or without minimal symptoms and asymptomatic higher risk patients ineligible for allogeneic stem cell transplantation, should be followed with a watch-and-wait strategy. There is no indication for JAK2 inhibitors in this group of patients. Follow up visits should be planned every four to six months.

Recommendations

- *A watch-and-wait strategy is the preferred option for paucisymptomatic myelofibrosis patients, ineligible for stem cell transplantation (Evidence level II, grade B).*
- *Low dose aspirin and hydroxyurea to normalise platelet and leukocyte counts should be considered in patients with a history of thrombosis or above 60 years of age (Evidence level II, grade B).*
- *Clinical trials with new agents are needed to try to modulate the biology of the disease and to delay progression.*

In the Belgian survey, the number of patients with constitutional symptoms was analysed according to the DIPSS risk scores (*Figure 1*). Only a minority of patients in advanced MF were paucisymptomatic. Moreover, a sub-analysis of the COMFORT-II trial, showed that advanced MF patients experience severe disease-related symptoms and have a diminished quality of life, comparable to patients with acute myeloid leukemia.[18] Therefore, there is a need for symptomatic treatment of MF patients living with a reduced quality of life for many years.[21]

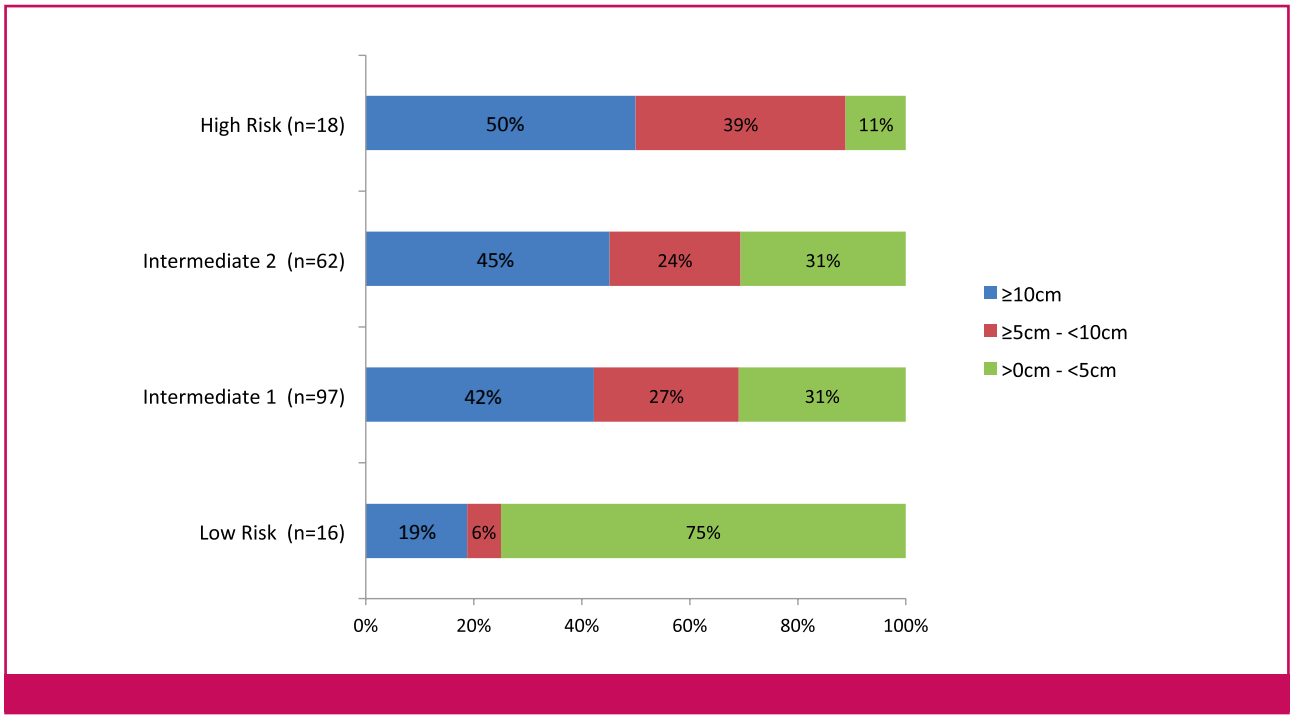

Figure 2. Distribution of patients with a palpable spleen according to DIPSS and spleen size.

Patients with MF are at risk of thrombosis at a rate similar to that reported in ET.[22] Aged above 60 and a history of thrombosis are the main risk factors for thrombosis. Hyperleukocytosis and JAK2 V617F positivity also probably count as risk factors. Patients above 60 or with a history of thrombosis should be treated with low dose aspirin, and with cytoreductive treatment if they present high platelet or white blood cell counts.

Symptomatic splenomegaly

Symptomatic or massive splenomegaly is the most common feature in MF. Splenomegaly may induce mechanical compression (responsible for early satiety, abdominal discomfort or leg edema), pain, splenic infarcts or refractory cytopenias. In end-stage MF patients, splenomegaly can go along with portal hypertension leading to ascites and variceal bleeding.[23,24]

Data of the Belgian survey indicated that 77% of the MF patients have a palpable spleen. In 41.9%, spleen size was ≥10 cm under the costal margin. The spleen size increases with the DIPSS score (*Figure 2*).

Different options are available to treat symptomatic splenomegaly in MF patients ineligible for transplantation. Until recently, hydroxyurea was first choice but JAK2 inhibitors are changing the landscape of management of splenomegaly in MF. In the Comfort II trial, 47% of the patients in the best available therapy (BAT)-arm received hydroxyurea and none reached a >35% spleen volume reduction, the endpoint of the trial.[18] However, in a retrospective analysis of 40 MF patients treated with hydroxyurea, a clinical improvement was seen in 40% of the patients, including a reduction in palpable spleen length of ≥50% in 30% and disappearance of palpable splenomegaly in 10% of the patients.[25] Responses to hydroxyurea last for an average of one year.

Ruxolitinib, a first-in-class JAK1 and JAK2 inhibitor, is very effective in reducing splenomegaly in both JAK2 V617F positive and negative MF patients. Two prospective randomised phase three trials compared the effect of ruxolitinib to placebo (COMFORT-I) or to BAT (COMFORT-II) in intermediate-2 or high risk MF patients.[17,18] The two studies reached their endpoint, which was a reduction of at least 35% in spleen volume, which corresponds approximately to a decrease of 50% of the palpable spleen length. The endpoint was reached in 41.9% (ruxolitinib) versus 0.7% (placebo) at six months in COMFORT-I, and 28% (ruxolitinib) versus 0 % (BAT) at 1 year for COMFORT-II. In the two studies, the majority of the patients had a reduction of their spleen size with ruxolitinib, even if they did not reach the endpoint. The effect of ruxolitinib on the spleen size was fast (within the first weeks) but the spleen regained its initial volume within one or two weeks upon ruxolitinib arrest. The effect of ruxolitinib on the spleen was

Figure 3. Distribution of MF patients according to spleen size and platelet count.

durable, since the median time of response was not reached at two year follow-up. Ruxolitinib is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and is available in Belgium in the context of clinical trials or a medical need program. Longer follow-up is needed to identify possible long-term side effects or on the other hand detect long term benefit on the biology of the disease.
The major haematological side effects of ruxolitinib are anaemia and thrombocytopenia. These side effects are manageable by dose interruption or modification and rarely led to discontinuation in the COMFORT trials. Usually, the haemoglobin level drops with a peak at eight to twelve weeks, then tends to stabilise at a new steady-state level. In Comfort-II, patients treated with ruxolitinib did not receive more erythrocyte transfusions than patients in the BAT arm. Due to the platelet-lowering effect of ruxolitinib, this medication is not routinely indicated for patients with less than 100 000 platelets/mm^3. In our Belgian survey, among the patients with a spleen length ≥10 cm below the costal margin, 16/81 (20%) had platelet counts lower than 100 000/mm^3 (*Figure 3*). If interruption of ruxolitinib is necessary, tapering the dose is recommended because of a possible rapid recurrence of systemic symptoms.

Clinical trials with other JAK1-2 inhibitors or JAK2 specific inhibitors are currently enrolling. These molecules may be a good option for patients with symptomatic splenomegaly and platelets below 100 000/mm^3 or resistant or intolerant to ruxolitinib. It is also important for the community to test other JAK inhibitors that could show different spectrum of efficacy or tolerability from ruxolitinib.

Splenectomy can alleviate the symptoms related to massive splenomegaly, but harbours significant morbidity and mortality. Laparoscopic splenectomy can be proposed to decrease morbidity, but can be difficult in patients with massive splenomegaly. Indications for palliative splenectomy are drug-resistant splenomegaly, symptomatic portal hypertension with oesophageal varices and transfusion dependent anaemia unresponsive to therapy. A thorough evaluation should be done to determine if the patient is an optimal candidate for surgery given that the complication rates are significant (overall 27.7% and 6.7% fatal).[24] Thrombosis of the splenoportal tract is a frequent complication of splenectomy, especially in patients with thrombocytosis. Hydroxyurea should be prescribed pre- and/or post-splenectomy to normalise platelet count and decrease the risk of thrombosis. Splenectomy is rarely performed in MF-patients nowadays and it is expected to become even more exceptional with the emergence of JAK2 inhibitors. In the Belgian MF survey, only 2% of the patients were splenectomised.

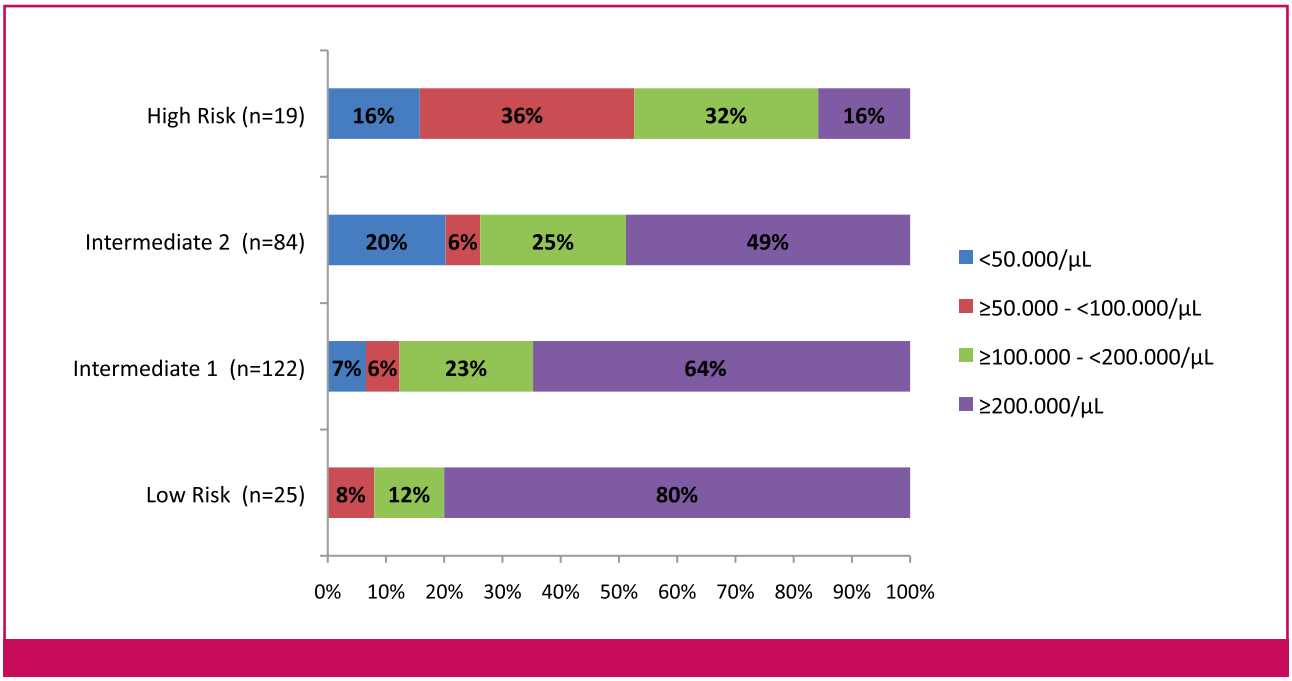

Figure 4. Distribution of platelet counts in MF patients according to DIPSS.

Splenic irradiation can be used in the palliative setting for relief of symptomatic splenomegaly but should be used with caution. Splenic irradiation can induce severe cytopenias and should be given at low dose (1 Gy in 5-10 fractions).[26] Responses are not durable. For symptomatic extramedullary haematopoiesis, on the other hand, radiotherapy is the treatment of choice.

Recommendations

- *In clinical trials, JAK inhibitors like ruxolitinib appear to be more effective than hydroxyurea to decrease the spleen size. They are the first choice for myelofibrosis patients with symptomatic splenomegaly that are refractory to hydroxurea or that are in advanced disease with more than 100 000/mm^3 platelets. Because long term data are still lacking, JAK inhibitors should not be used out of the context of clinical trials in low risk patients (Evidence level I, grade A).*
- *Hydroxyurea also reduces splenomegaly and the dose should be escalated progressively to an effective dose without inducing significant cytopenia. The effect of hydroxyurea is transient (Evidence level II, grade B).*
- *Clinical trials with new JAK inhibitors should be encouraged.*
- *Splenectomy and splenic irradiation harbour significant morbidity and mortality and therefore should be reserved for a selected group of patients (Evidence level II, grade C).*

Symptomatic anaemia, thrombocytopenia and general haematological characteristics of progressive MF

Anaemia is present in a high proportion of MF patients. Anaemia results from a defective haematopoiesis, but also hemodilution related to splenomegaly can explain anaemia. In addition, a low grade haemolysis can occur. There are no data to demonstrate that interfering with anaemia will improve the outcome of patients, but erythropoiesis-stimulating medication can be beneficial to reduce anaemia-related symptoms. However, transfusions often remain the only strategy to reduce symptomatic anaemia.

Several agents have been used to treat MF-associated anaemia. Reponses are usually discrete, unpredictable and of short duration (no longer than one year). Erythropoiesis-stimulating agents (ESAs) should be considered in patients with low endogenous EPO levels (<125 UI/L) but are not reimbursed in this context in our country. Forty to fifty percent of the patients will respond to ESA, essentially patients with low transfusion requirement. A starting dose of 10 000 units of rEPO three times a week or 150 µg of darbopoietin weekly are usually recommended. The dose can be doubled after one or two months if no response is observed.[27-29]
Androgens or danazol show response rates of about 30%. Starting dose of danazol is 200 mg daily, with a gradual dose escalation to 600 mg or 800 mg for patients above

80 kg. Responses can be slow and six months of treatment is required before considering a therapy failure. After six months, danazol will be progressively tapered to the minimum active dose in responding patients. Close follow-up of liver enzymes, prostate or hepatic malignancies and left ventricular function is necessary in these patients.[30]

Low dose thalidomide (50 mg/d) with or without combining tapering doses of prednisone and low dose lenalidomide improves anaemia in about 20%.[31,32] These immunomodulatory drugs (IMIDs) are often poorly tolerated, essentially because of neuropathy for thalidomide and myelosuppression for lenalidomide. These medications occasionally decrease the spleen size. For the few MF patients with an isolated 5q, lenalidomide is the first choice of treatment.[26]
Pomalidomide, a third generation IMID, induced 25% of response to anaemia in a phase two randomised study.[33] MF patients with the V617FJAK2 mutation and palpable spleen sizes <10 cm seem to be the best candidates for this drug. A phase three trial comparing pomalidomide versus placebo (RESUME trial) is now closed for recruitment.

Thrombocytopenia is often present in MF patients and it has been added as a negative prognostic factor in the DIPSS Plus scoring system.[7] Except for anecdotal platelets responses to danazol, splenectomy, thalidomide or lenalidomide, no treatment is able to increase the platelet count in MF. In the Belgian survey, grade 3-4 thrombocytopenia does not seem to be that common: 89% of the patients had platelet counts ≥50000/μL (with 57% showing thrombocytes ≥200000/μl). The proportion of patients with a low platelet count increased with the IPSS and DIPSS risk category (*Figure 4*), in line with the development of thrombocytopenia as the disease progresses.
Some MF patients have increased leukocyte counts and thrombocytosis. This excessive myeloproliferation probably goes along with an increased risk of thrombosis, and can lead to constitutional symptoms and contribute to splenomegaly. In symptomatic patients or patients at risk of thrombosis, myelosuppressive therapy is indicated. Hydroxyurea is the drug of choice. JAK2 inhibitors also reduce excessive high blood cell counts.

Because of the lack of data on anagrelide in MF, it should be used with caution in this disease. Conventional pegylated interferon is able to control the cell count in low risk MF patients but is usually poorly tolerated in advanced patients. Unfortunately, this drug is not reimbursed in Belgium for non-CML MPN patients.

Recommendations

- *Erythropoiesis-stimulating agents* should be tried in patients with symptomatic anaemia and erythropoietin level <125 U/ml (Evidence level II, grade B).*
- *Lenalidomide* is the treatment of choice for the few patients with isolated 5q (Evidence level II, grade C).*
- *In patients with symptomatic anaemia not responding to erythropoiesis-stimulating agent or patients with erythropoietin level >125 U/ml, danazol, thalidomide or lenalidomide with or without prednisone should be considered as therapeutic options, but can induce significant morbidity (Evidence level II, grade B).*
- *High platelet and leukocyte counts should be treated with hydroxyurea, especially in patients above 60 years of age or with a history of thrombosis. JAK inhibitors are also able to control excessive high blood counts (Evidence level II, grade B).*

** Not reimbursed in Belgium but available through compassionate use or medical need programs.*

Constitutional symptoms

Constitutional symptoms (CS) have an important impact on quality of life of MF patients and have been associated with shortened survival.[34] Consequently fever, drenching night sweats and weight loss (>10%) are prognostic factors in the different prognostic scores.

About one third (34,5%) of patients reported in the Belgian MF survey suffered from at least one of these symptoms. Previous reports have shown similar proportions (26,4%, 35%).[5,7] These symptoms are mainly present in patients with advanced disease but also in patients with lower risk (*Figure 1*). The spleen is palpable in a slightly higher proportion of patients with CS (72/86; 84%) compared to those without CS (121/164; 74%). Moreover, CS were associated with a spleen size >5 cm below the costal margin (71% of patients with versus 42% of patients without CS). Remarkably, even in the group without splenomegaly, 23,5% mentioned CS. Conventional agents like hydroxyurea or low dose prednisolone only show modest benefits against CS. This is illustrated in the COMFORT-II trial as none of the patients in the BAT arm showed improvement of their QoL-scores.[18]

JAK inhibitors show rapid improvement of symptoms like fatigue, CS, pain, dyspnoea, insomnia and appetite loss. The majority of patients gained weight. In the COMFORT II trial, the patients treated with ruxolitinib showed significant improvements in MF-associated symptoms at week 48, as measured by the EORTC QLQ-C30 or FACT-Lym scores.[18]

Recommendations

- *Myelofibrosis patients with advanced disease and severe constitutional symptoms should be treated with ruxolitinib if their platelet count is above 100 000/mm^3 or another JAK inhibitor in the context of a clinical trial (Evidence level I, grade A).*
- *Symptomatic, low risk myelofibrosis patients could be treated with JAK inhibitors, but only in the setting of a clinical trial because of the lack of long term data in this context (Evidence level II, grade C).*

Conclusion

Diagnosis and treatment of Philadelphia-chromosome negative MPN is a rapid evolving domain. The discovery of the V617F JAK2 mutation in 2005 was the start of a renewed interest in MPN and multiple mutations have been described since and are still appearing. The recent availability of JAK inhibitors has lead to significant quality of life improvements for myelofibrosis patients. New prognostic models and scores have been developed. As a consequence of these changing diagnostic and therapeutic criteria in MF, the need for updated guidelines for the management of MF became apparent and are presented in this paper.

In a recently conducted survey, eighteen Belgian Haematology centres collaborated to gather data of 250 MF patients, with the aim to describe quantitative data on the disease-specific characteristics in Belgian MF patients, taking into account the international prognostic scores (IPSS or DIPSS). Some of the results of this survey are presented throughout this paper, in conjunction with presenting the symptom-related management guidelines of MF patients.

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