clinical practice guidelines

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Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence

According to the 2008 World Health Organization (WHO) classification, classical Philadelphia chromosome/BCR-ABL negative chronic myeloproliferative neoplasms (MPNs) include polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF) [1]. The reported worldwide annual incidence rate of MPNs ranges from 0.44 to $5.87/10^5$, with the lowest incidence being reported in Japan and Israel [2]. These great ranges may reflect racial/geographic differences as well as differences in study design, diagnostic criteria and methods of reporting, among others. The estimated incidence rate in Europe is $0.4–2.8 \times 10^5$/year for PV, $0.38–1.7 \times 10^5$/year for ET and $0.1–1 \times 10^5$/year for PMF [2]. There are few reliable estimates of the prevalence [2, 3]. The last is likely to be rising due to earlier diagnosis and trends towards prolonged survival [4]. The reported median age at diagnosis ranges from 65–74 years for PV, 64–73 years for ET, and 69–76 years for PMF [2].

diagnosis and pathology/molecular biology

To achieve the most accurate diagnosis possible, the 2008 WHO classification is recommended. It is based upon standardised morphological features, ideally using specimens obtained before treatment, and is integrated with haematological, molecular and clinical diagnostic criteria (Table 1). For full details and images of classical morphological features, the reader is referred to the WHO publication [1]. European consensus-based criteria for grading of cellularity and bone marrow (BM) fibrosis should be followed (Table 2) [6].

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In PV, classical BM features are a moderate to overt increase in age-matched cellularity, due to a trilineage proliferation (panmyelosis) of erythroid and granulocytic precursors and megakaryocytes in variable proportions. Megakaryocytes are characterised by a pleomorphic appearance due to the variability in sizes, from small to giant cells, without gross abnormalities of maturation. There may be minimal (grade 1) reticulin fibrosis, which is very rarely grade 2.

In ET, age-adjusted cellularity is normal or sometimes slightly increased; there is no left-shifted neutrophil granulopoiesis. Any case with a mild to moderate panmyelosis is suspicious for early PV rather than ET. Megakaryocytes have increased in number and are randomly distributed within the BM, with scattered forms or a few loose clusters. Large to giant mature megakaryocytes with extensively folded (staghorn-like) nuclei and mature cytoplasm are in the majority. Gross disturbances of the histologic topography or extensive dense clustering of megakaryocytes should not be detectable. There is no substantial increase of reticulin fibres. The WHO classification suggests that these features clearly distinguish ET from pre-fibrotic/early PMF; however, minor diagnostic criteria should also be present in order to assign this diagnosis (Table 1).

In the initial phases of PMF, the BM is often hypercellular with prominent granulocytic and megakaryocytic proliferation, frequently with a reduction of erythroid precursors. If reticulin fibrosis is present, grade 1 is allocated. Megakaryopoiesis is characterised by the extensive formation of loose to dense clusters of megakaryocytes, with abnormal localisation toward the endosteal borders. Megakaryocyte anomalies include a high degree of cellular atypia (from small to giant forms), abnormal nuclear folding and an aberrant nuclear cytoplasmic ratio created by large, bulbous and hyperchromatic cloud-shaped nuclei. Naked (bare) megakaryocytic nuclei are often visible.

Overall, the megakaryocytes in PMF show a more pronounced degree of atypia than in other MPN subtypes. The more advanced fibro-osteosclerotic phases of PMF are characterised by grade ≥2

Table 1. The WHO diagnostic criteria for Philadelphia chromosome-negative chronic myeloproliferative neoplasms [1]

	Polycythaemia vera (PV)	Essential thrombocythaemia (ET)	Primary myelofibrosis (PMF)
Major criteria	1. Haemoglobin >18.5 g/dl (men) >16.5 g/dl (women) or [a] any other evidence of increased red cell volume	1. Platelet count ≥450 × 10^9/l	1. Megakaryocyte proliferation and atypia[b] accompanied by either reticulin and/or collagen fibrosis, or [c]
	2. Presence of *JAK2*V617F or *JAK2* exon 12 mutation	2. Megakaryocyte proliferation with large and mature morphology	
		3. Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	2. Not meeting WHO criteria for CML, PV, MDS or other myeloid neoplasm
		4. Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive thrombocytosis	3. Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive BM fibrosis
Minor criteria	1. BM trilineage myeloproliferation		1. Leukoerythroblastosis
	2. Sub-normal sEPO level		2. Increased serum LDH level
	3. Endogenous erythroid colony growth		3. Anaemia
			4. Palpable splenomegaly

[a]Hb or HCT >99th percentile of reference range for age, sex or altitude of residence or red cell mass >25% above mean normal predicted or Hb >17 g/dl (men)/>15 g/dl (women) if associated with a sustained increase of ≥2 g/dl from baseline that cannot be attributed to correction of iron deficiency.
[b]Small to large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.
[c]In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF).

PV diagnosis requires meeting either both major criteria and one minor criterion or the first major criterion and two minor criteria. ET diagnosis requires meeting all four major criteria. PMF diagnosis requires meeting all three major criteria and two minor criteria.
Note: mutations in calreticulin (*CALR*) will be included as major diagnostic criteria for ET and PMF in the upcoming (2015) revised WHO classification [5].
BM, bone marrow; WHO, World Health Organization; CML, chronic myelogenous leukaemia; MDS, myelodysplastic syndromes; LDH, lactate dehydrogenase; sEPO, serum erythropoietin; Hb, haemoglobin; HCT, haematocrit.

Table 2. European consensus on the grading of myelofibrosis (MF) [6]

MF—0 Scattered linear reticulin with no intersection (cross-overs) corresponding to normal bone marrow
MF—1 Loose network of reticulin with many intersections, especially in perivascular areas
MF—2 Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF—3 Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

Fibre density should be assessed in haematopoietic (cellular) areas.
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reticulin deposition, and the appearance of coarse bundles of collagen fibres. Additional features include endophytic bone formation (osteosclerosis) associated with extension of adipose tissue. Dilated marrow sinuses with intraluminal haematopoiesis, especially made up of megakaryocytes, are often seen.

The morphological hallmark of post-polycythaemia vera myelofibrosis (PPV-MF) and post-essential thrombocythaemia myelofibrosis (PET-MF) is overt reticulin and collagen fibrosis of the BM. Cellularity varies, but hypocellularity is common. Clusters of megakaryocytes (often with hyperchromatic and abnormal nuclei) are prominent, while erythropoiesis and granulopoiesis are decreased. Osteosclerosis may occur. However, these findings must be integrated with other features to achieve a diagnosis (Table 3).

Although a number of clinicopathological studies have demonstrated that a reliable morphological differentiation can be achieved with high consensus rates [8–10], both the reproducibility and the clinical usefulness of the WHO classification of MPNs remain controversial issues, especially concerning the distinction between ET and pre-fibrotic/early myelofibrosis (MF) as well as initial cases of PV from ET or even PMF [11, 12]. To avoid incorrect classification, comprehensive evaluation and, if necessary, re-evaluation of patients are suggested. This also ensures that the patient is not unnecessarily diagnosed as 'MPN-unclassified'.

MPNs are characterised by somatic recurrent mutations and are included as the main criteria in the 2008 WHO classification (Table 1), for which a further revision is expected in the future due to the newly discovered calreticulin (*CALR*) mutations [5]. These mutations include the Janus kinase (*JAK*) *2*V617F mutation, found in ≥95% of PV and ∼60% of ET and PMF patients. 3%–5% of ET and 5%–8% of PMF patients have point mutations at codon 515 of the gene encoding the thrombopoietin receptor *MPL* (W>L, K or A).

Abnormalities (deletions/duplications/substitutions) located in exon 12 of *JAK2* are detected exclusively in 2%–4% of PV.

Table 3. Diagnostic criteria for post-polycythaemia vera myelofibrosis (PPV-MF) and post-essential thrombocythaemia myelofibrosis (PET-MF) according to the International Working Group for Myeloproliferative Neoplasm Research and Treatment (IWG-MRT) [7]

PPV-MF	PET-MF
Required criteria (both required):	
1. Documentation of a previous diagnosis of PV as defined by the 2008 WHO criteria	1. Documentation of a previous diagnosis of ET as defined by the 2008 WHO criteria
2. Bone marrow fibrosis grade 2–3 (on a 0–3 scale) or grade 3–4 (on a 0–4 scale)	2. Bone marrow fibrosis grade 2–3 (on a 0–3 scale) or grade 3–4 (on a 0–4 scale)
Additional criteria (≥2 required):	
Anaemia or sustained loss of requirement for phlebotomy in the absence of cytoreductive therapy	Anaemia and a Hb ≥2 g/dl decrease from baseline Hb level
Leukoerythroblastic peripheral blood picture	Leukoerythroblastic peripheral blood picture
Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm from the LCM, or the appearance of a newly palpable splenomegaly	Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm from the LCM, or the appearance of a newly palpable splenomegaly
Development of ≥1 of the constitutional symptoms (>10% weight loss in 6 months, night sweats, unexplained fever >37.5°C)	Development of >1 of the constitutional symptoms (>10% weight loss in 6 months, night sweats, unexplained fever >37.5°C)
	Increased lactate dehydrogenase

WHO, World Health Organization; LCM, left costal margin; Hb, haemoglobin; PV, polycythaemia vera; ET, essential thrombocythaemia.
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About 60%–80% of *JAK2* and *MPL* un-mutated patients with ET and PMF have mutations in the exon 9 of *CALR*. Therefore, virtually all patients with PV have a mutation in *JAK2*. Conversely, 10%–15% of ET and PMF patients remain molecularly uncharacterised, and are operationally defined as 'triple negative' for the three phenotypic driver mutations. The presence of any of these mutations excludes reactive forms of erythrocytosis, thrombocytosis and MF, but does not indicate a specific MPN subtype. These mutations can be found using methods such as conventional sequencing, qualitative and quantitative polymerase chain reaction (PCR) and high-resolution melting analysis (may have a sensitivity of 1% and higher). Whole blood or purified granulocytes are harvested and tested; the latter is preferred in cases with low mutation burden, as is often the case with *JAK2* exon12 mutations. Genotyping should be obtained at diagnosis. It is not recommended to measure the mutation burden serially during follow-up or to assess response to treatment, except following allogeneic stem-cell transplantation (alloSCT) and, possibly, interferon (IFN) treatment. In such instances, a detection limit of *JAK2*V617F allele burden of ≤0.1% is recommended [13].

achieving an accurate diagnosis

Accurate differentiation among the three unique MPN subtypes as well as the exclusion of reactive conditions (in mutation-negative patients only) and disorders such as myelodysplasia and chronic myeloid leukaemia (CML) are critical for appropriate prognosis and therapy decision making. It is not acceptable to use the generic diagnostic label 'MPN' alone [I, A]. The 2008 WHO diagnostic criteria for MPN outlined in Table 1 should be followed strictly [1]. Any patient with suspected MPN should be tested for the three driver mutations [I, B]. A simplified diagnostic algorithm is presented in Figure 1. A diagnosis of PPV-MF or PET-MF is made using the criteria described by the International Working Group for Myeloproliferative Neoplasm Research and Treatment (IWG-MRT) (Table 3).

assessment of prognosis

Any patient newly diagnosed with MPN should be categorised at baseline according to the risks associated with the disease [I, B]. It must be realised that the prognostic scoring systems used for risk-adapted therapy in PV and ET are based on the likelihood of patients developing thrombotic complications. These complications are the leading cause of morbidity and mortality in PV and ET patients. Scores predicting for overall survival in PV and ET are also available, yet considering the long survival of these disorders, they do not currently impact treatment decisions [14, 15]. The recommended prognostic scoring system for PV and ET is based upon two variables: age >60 years and previous history of thrombosis. These variables separate patients into low- or high-risk categories (Table 4). In ET, an intermediate-risk group is sometimes advocated. However, this group is variably defined and there is no clear evidence of how to manage patients in this category. Thrombocytosis (>1000 × 10^9/l) is a risk factor for haemorrhage, and advocates caution for the use of aspirin. Extreme thrombocytosis (>1500 × 10^9/l) is regarded as an indication for therapy in ET, and less frequently in PV. Improved risk stratification is desirable, but any new risk stratification should be robust, easily measurable and ideally validated in a prospective manner.

Since the median survival in PMF is ∼6 years, ranging from <2 to >10 years, the relevant end point for current prognostic scoring systems in PMF is represented by survival (Table 5). The International Prognostic Scoring System (IPSS) [18] is used at the time of diagnosis to outline four risk categories (low, intermediate-1, intermediate-2 and high risk), with median survival of 135, 95, 48 and 27 months, respectively. The 'dynamic' IPSS

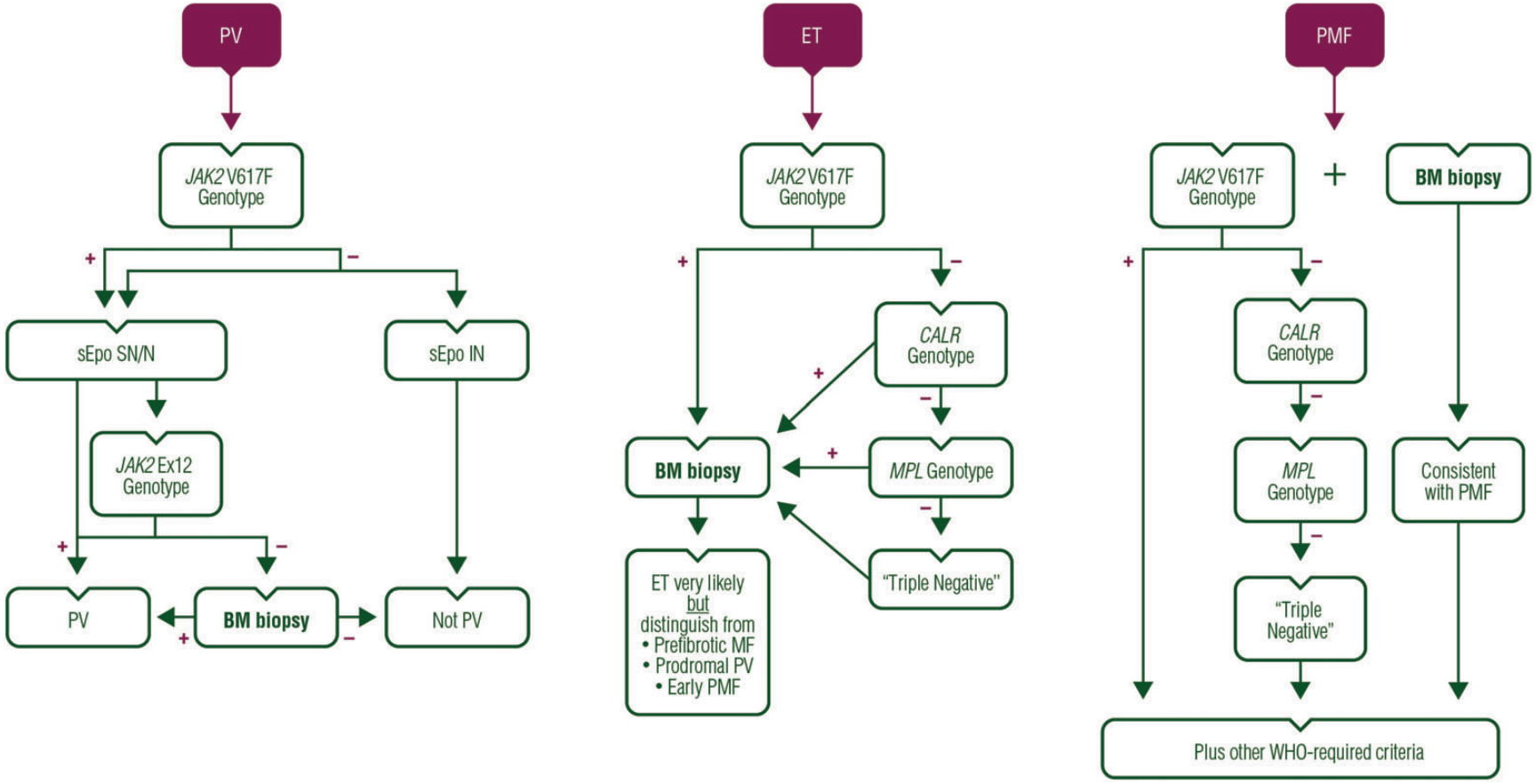

Figure 1. Diagnostic algorithm for MPN, based on the 2008 WHO criteria. PV, polycythaemia vera; ET, essential thrombocythaemia; PMF, primary myelofibrosis; SN, sub-normal EPO level; N, EPO levels in the normal range; IN, increased EPO level above normal range; BM biopsy, bone marrow biopsy; WHO, World Health Organization.

(DIPSS) [19], which utilises the same variables as the IPSS, is employed during follow-up. A refinement is represented by DIPSS-plus score [20] that incorporates thrombocytopaenia, transfusion requirements and abnormal cytogenetics (Table 5). The role of *CALR* [21] and other mutations (i.e. *EZH2*, *ASXL1*, *SRSF2*, *IDH1/2* mutations), comprising a high-molecular risk category in PMF [22], has been underscored but has yet to be incorporated in an updated prognostic score. Appropriate risk stratification in PMF has relevance for risk-adapted therapy, particularly for alloSCT. These scores are commonly used for PPV-MF and PET-MF. It should be underlined that they have not been validated in such a context, and their appropriateness has been questioned [23].

Table 4. Risk stratification and risk-adapted therapy in polycythaemia vera (PV) and essential thrombocythaemia (ET) [16, 17]

Risk category	Risk variables	Therapy	
		PV	ET
Low	• Age <60 years • No thrombosis history	• Phlebotomy, *and* • Correction of CV risk factors, *and* • Low-dose aspirin[a]	• Correction of CV risk factors, *and* • Low-dose aspirin[a]
High	• Age ≥60 years *and /or* • Thrombosis history	• Cytoreduction, *and* • Correction of CV risk factors, *and* • Low-dose aspirin[a] • Phlebotomy if required	• Cytoreduction, *and* • Correction of CV risk factors, *and* • Low-dose aspirin[a]

[a]Depending on the thrombosis type, oral anti-coagulation instead of low-dose aspirin.
CV, cardiovascular.

management

Treatment aims are to reduce the risk of thrombosis and haemorrhage, control symptoms and perhaps reduce the risk of progression (Figure 2). Cure is not presently possible, except in selected MF patients who are successfully receiving alloSCT. All patients should be informed regarding the disease course, and vascular risk factors such as smoking should be aggressively managed.

polycythaemia vera

PV therapy should address both short- and long-term objectives (Figure 2A). In the short-term, therapeutic aims are to reduce the risk of occurrence and recurrence of thrombosis. The long-term objective is to reduce the risk of evolution to MF, myelodysplastic syndrome (MDS) and/or acute myeloid leukaemia (AML) [16]. Risk stratification (Table 4) aims at selecting the patients with a low risk of vascular events. PV is associated with elevated haematocrit (HCT); with these patients, phlebotomy is carried out to control the HCT and low-dose aspirin is used, as it may delay the need for cytoreductive therapy.

first-line therapy. Phlebotomy can be an emergency therapy at diagnosis, in patients presenting with very high HCT and clinical signs of hyperviscosity, as well as a long-term maintenance

Table 5. Risk stratification in primary myelofibrosis (MF)

Variable	IPSS [18]		DIPSS [19]		DIPSS-plus [20]	
Age >65 years	✓		✓		✓	
Constitutional symptoms	✓		✓		✓	
Haemoglobin (Hb) <10 g/dl	✓		✓		✓	
Leukocyte count >25 × 10^9/l	✓		✓		✓	
Circulating blasts >1%	✓		✓		✓	
Platelet count <100 × 10^9/l					✓	
RBC transfusion need					✓	
Unfavourable karyotype[a]					✓	
	1 point each		1 point each but Hb = 2		Calculated by the DIPSS score (Int 1 = 1, Int 2 = 2, High = 3) plus one additional point for each of the three additional variables	
Risk group	Points	Median survival (years)	Points	Median survival (years)	Points	Median survival (years)
Low	0	11.3	0	n.r.	0	15.4
Intermediate-1	1	7.9	1–2	14.2	1	6.5
Intermediate-2	2	4.0	3–4	4	2–3	2.9
High	≥3	2.3	5–6	1.5	≥4	1.3

[a]Unfavourable karyotype includes +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, 11q23 rearrangements.
IPSS, International Prognostic Scoring System; DIPSS, dynamic International Prognostic Scoring System; RBC, red blood cell; Int, intermediate; n.r., not reached.

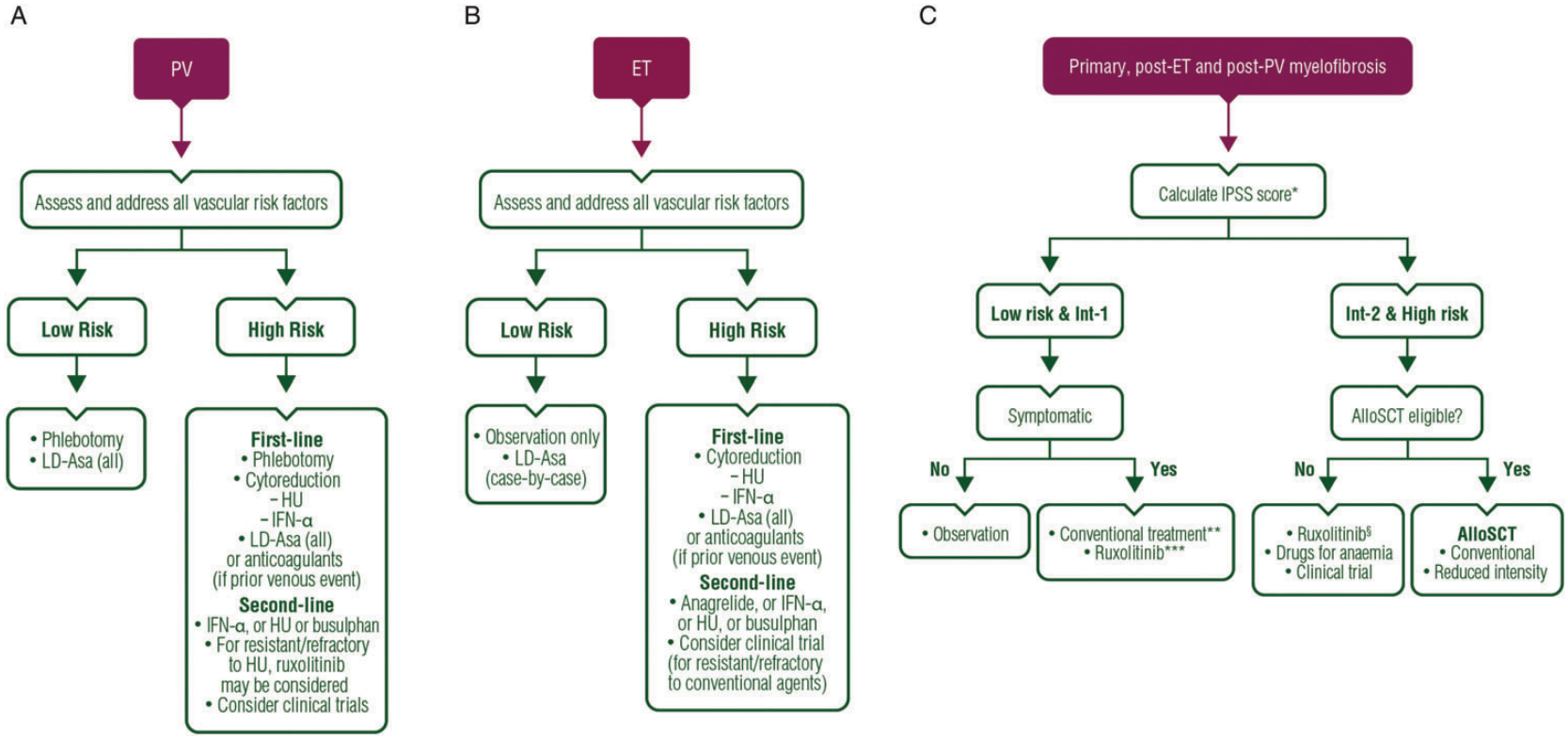

Figure 2. Therapeutic algorithms for polycythaemia vera, essential thrombocythaemia, and myelofibrosis. * Dynamic IPSS and Dynamic IPSS-plus after diagnosis. **Hydroxyurea for symptomatic splenomegaly in countries where ruxolitinib is not approved for low-risk patients. If anaemia is the problem, erythropoietin, corticosteroids, danazol, immunomodulators or splenectomy. ***For patients presenting with symptomatic splenomegaly and/or constitutional symptoms if allowed by the label. §For patients presenting with symptomatic splenomegaly and/or constitutional symptoms. PV, polycythaemia vera; ET, essential thrombocythaemia; LD-Asa, low-dose aspirin; HU, hydroxyurea; INF-α, interferon-α; IPSS, International Prognostic Score System; Int, intermediate; AlloSCT, allogeneic stem cell transplantation.

therapy to control the HCT [I, A]. The optimal target of HCT levels for reducing vascular events was a matter of debate, but, a recent multicentre, randomised clinical trial (CYTO-PV) showed that the HCT should be maintained strictly below 45% to efficiently reduce the risk of thrombotic events [I, A] [24]. Low-dose aspirin is the second cornerstone of PV therapy [I, A]. It has been shown in the European Collaboration on Low-dose Aspirin in Polycythaemia Vera (ECLAP) study, a large European double-blind, placebo-controlled, randomised trial, to significantly reduce a primary combined end point, including: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and major venous thromboembolism [25].

A cytoreductive drug should be prescribed in high-risk PV patients, i.e. >60 years and/or with a history of a vascular event. In 2011, the European LeukemiaNet (ELN) published recommendations for the management of PV, concluding that hydroxyurea (HU) [II, A] and IFN-α [III, B] were recommended as first-line treatments for high-risk patients [16]. HU is a well-known cytoreductive agent, with good efficacy and tolerance in the majority of patients. In the unique randomised trial comparing HU with another cytoreductive drug (pipobroman) in PV, the cumulative incidence of AML/MDS at 10, 15 and 20 years was 6.6%, 16.5% and 24% in the HU arm and 13%, 34% and 52% in the pipobroman arm, respectively ($P = 0.004$) [26]. Other studies from registry data and prospective analysis with shorter follow-up failed to attribute a clear leukaemogenic risk to HU [17, 27]. Overall, there is no definitive evidence for (or against) a leukaemogenic risk of HU, but it should be emphasised that this risk may appear after prolonged exposure to this drug. Thus, it seems reasonable to adopt a conservative approach and to consider alternative treatments in young subjects, and in those previously treated with other myelosuppressive agents. IFN-α has been shown to induce a high rate of haematological response and to significantly reduce the malignant clone, as shown by the percentage of mutated allele *JAK2*V617F in two phase II studies [28, 29]. However, this drug (in any of its various presentations) is not approved for the treatment of PV. Two phase III studies comparing HU to pegylated forms of IFN-α are ongoing in the United States and Europe. These studies should help to better define the efficacy and tolerance of each drug in the short term [30]. Whenever possible, patients should be recruited into these studies [II, B]. Aquagenic pruritus is a disabling symptom in some PV patients: IFN-α or JAK2 inhibitors can be used to treat this symptom. Other options include antihistamines, selective serotonin reuptake inhibitors and PUVA (psolarens + ultraviolet A) therapy [IV, B] [31, 32].

second-line therapy. The choice of second-line myelosuppressive drugs for PV should be carefully evaluated because some drugs administered after HU may enhance the risk of acute leukaemia [II, B] [33]. Finally, in selected patients, alkylating agents like busulfan may be useful when other drugs have failed or are contraindicated, although they are characterised as inducing an increased leukaemogenic risk [III, C] [16]. In PV, a phase III study showed the use of ruxolitinib was superior, compared with the best available therapy, to control HCT and splenomegaly in PV patients who are resistant or intolerant to HU. These results suggest that ruxolitinib could be a new option as a second-line therapy in PV [I, A] [34].

essential thrombocythaemia

Aspirin in ET has never been evaluated in a randomised, controlled trial, and there is a concern that bleeding is a particular risk for ET patients with extreme thrombocytosis ($>1000 \times 10^9$/l) [35]. Low-dose aspirin is recommended in the setting of high-risk ET patients without a clear contraindication to this therapy [III, B]. For low-risk ET patients, a retrospective analysis suggested that only those who are either *JAK2V617F*-positive or have cardiovascular risk factors may benefit from anti-platelet therapy [36]. Pending further data, we recommend low-dose aspirin for low-risk ET patients, since thrombosis remains the major clinical hazard [III, B] (Figure 2B).

The choice of the most appropriate first-line cytoreductive therapy for high-risk ET is based on three randomised trials [37–39]. There is a debate regarding whether HU, anagrelide or IFN-α should be the treatment of choice. In addition, there is an increased interest in 'pegylated' forms of IFN. HU versus no myelosuppressive therapy significantly reduced the rate of thrombosis in high-risk ET patients, most of whom received anti-platelet prophylaxis with aspirin or ticlopidine [37]. The use of anagrelide versus HU has been evaluated in the PT-1 study and the non-inferiority ANAHYDRET study. Anagrelide was equivalent to HU in reducing platelet counts in both studies. In the PT-1 study, an excess of arterial thrombosis was seen in the anagrelide arm compared with HU [38]. However, in the ANAHYDRET, study equivalence was reported [39]. The use of HU and low-dose aspirin as first-line therapy for high-risk ET is recommended, but in specific groups of patients, IFN or sometimes anagrelide may be appropriate [I, B]. Whenever possible, patients with ET should be enrolled in randomised studies evaluating HU compared with IFN. According to current label approvals in Europe, anagrelide may be used as second-line therapy for patients who are resistant or intolerant to HU. IFN or busulfan are also options available in this setting. The use of cytotoxic agents, in the youngest patients and/or especially in combination, should be avoided where possible [III, B]. In the presence of extensive thrombocytosis ($>1.500 \times 10^9$/l), the benefits of anti-platelet agents should be balanced against the risks of haemorrhages due the occurrence of acquired von Willebrand disease [35].

myelofibrosis

Since there is no curative therapy other than alloSCT for PMF and PPV-/PET-MF, treatment is essentially palliative and is generally guided by the predominant symptoms, anaemia and splenomegaly (Figure 2C).

anaemia. A haemoglobin <10 g/dl usually triggers consideration of treatment, but there are individual variations depending upon age and comorbidities. One of the first options is erythropoiesis-stimulating agents, which produce improvements in 23%–60% of patients [40, 41]. Response is often restricted to patients with inadequate erythropoietin levels (<125 mU/ml), and less frequently when there is significant splenomegaly or transfusion dependence. If no response is obtained at three

months, treatment should be stopped [III, B]. Androgens such as nandrolone, fluoxymesterone, methandrostenolone and oxymetholone improve anaemia in 30%–60% of patients [IV, B]. Similar results with less toxicity are obtained with danazol, with the overall response rate being 35% [III, B] [42]. The recommended dose is 400–600 mg daily maintained for at least 6 months, then progressively reduced to the minimum necessary for maintenance. Immunomodulating drugs may also be useful in managing anaemia but are frequently withdrawn early, due to toxicity. Low-dose thalidomide combined with oral prednisone provides a 23%–29% response [III, C] [43]. Lenalidomide, combined with low-dose prednisone taper, produces a 19% response [III, C] [44]. Lenalidomide as a single agent is the treatment of choice for MF patients with 5q deletion [V, C] [45]. Splenectomy can be useful in patients with transfusion-dependent anaemia refractory to drug therapy [IV, B] [46], but needs careful consideration due to complication rates (see below). Corticosteroids alone may also be used for the management of refractory anaemia in patients unresponsive to the above drugs, and who are not eligible for alloSCT or splenectomy. Corticosteroids used alone are often observed to result in modest haemoglobin increases and improvements in patient well-being [V, C].

splenomegaly and extra-medullary haematopoiesis. Traditionally, treatment of splenomegaly was not instituted before the appearance of associated symptoms, particularly due to the inherent risk of worsening cytopaenias. HU was previously the first-line therapy for symptomatic splenomegaly, with an overall response of 40% [IV, B] [47]. However, published experience suggests that after 1 year of treatment, ~80% of patients require an alternative therapy. The use of HU is now largely superseded by JAK inhibitors (see below). Splenectomy is indicated in patients with large and painful splenomegaly where JAK inhibitors are not available or prove ineffective [46]. Splenectomy requires an experienced surgical team and critical care support to minimise the risks associated with the procedure; a perioperative mortality rate of 5%–10% and a morbidity rate up to 25% can be expected [IV, D] [46]. Splenic irradiation can also be applied in patients who do not tolerate JAK inhibitors and are poor candidates for surgery [IV, D] [48]. However, benefit is transient and involves the risk of severe cytopaenias; therefore, its routine use is not recommended. Low-dose radiation is the therapy of choice for symptomatic extra-medullary haematopoiesis in places other than the spleen and liver, as well as for MF-associated pulmonary hypertension, due to extra-medullary haematopoiesis [IV, B] [49].

JAK inhibitors. The JAK inhibitors act mainly by inhibiting dysregulated JAK-STAT signalling, present in all MF patients. They are not selective of the mutated JAK2; therefore, they are indicated in both *JAK2*-mutated and *JAK2*-unmutated MF. Ruxolitinib, an oral JAK1/JAK2 inhibitor, is the first in-class drug approved for MF treatment [50]. Thrombocytopaenia is a main adverse event observed with JAK inhibitors, and worsening anaemia is often seen, especially at the beginning of therapy. These drugs are also associated with an increased risk of infection. Spleen reduction and symptom control are usually dramatic but are also drug- and dose-dependent.

It has been reported that sudden ruxolitinib withdrawal can provoke a shock-like syndrome, due to the re-emergence of the suppressed inflammatory cytokines [51]. Though this side-effect is rare, abrupt interruption should be avoided and withdrawal of the drug should be tapered.

Two phase III studies compared ruxolitinib with placebo (COMFORT-I) [52] or best available therapy (COMFORT-II) [53]; both attained the primary end point of ≥35% reduction in spleen volume by imaging techniques at 24 or 48 weeks of treatment, respectively [I, A]. The effect on *JAK2*V617F allele burden was modest [54]. A survival advantage for patients treated with ruxolitinib was first shown from historical comparison with matched MF populations [55, 56]. Extended follow-up of the phase III studies indicated a survival advantage for patients on ruxolitinib [54]. However, there is little evidence of a disease-modifying effect. Other JAK inhibitors are currently being studied in clinical trials, although several trials have been withdrawn due to emergent neurological toxicity. The precise mechanism for this toxicity is unclear but merits close monitoring.

stem-cell transplantation. AlloSCT is currently the only curative treatment approach for MF, resulting in resolution of BM fibrosis, molecular remission and restoration of normal haematopoiesis [57, 58]. Depending on the disease status, patient's performance status, comorbidities and donor availability, ~40%–70% of patients can be cured [57, 58]. Careful patient selection is mandatory, due to the inherent risks of alloSCT. Patients with PV or ET are not candidates for alloSCT, unless their disease has transformed into MF or secondary acute leukaemia [59]. Results with completely matched, related and unrelated donors are superior to those with human leukocyte antigen-mismatched donors [57, 60]. Reduced-intensity conditioning regimens resulting in lower therapy-related complications have broadened the availability of alloSCT to older patients, but a direct comparison to standard myeloablative conditioning is lacking [57, 59]. According to ELN recommendations, it is justified to offer alloSCT to eligible patients with MF whose median survival is expected to be <5 years. This includes patients with intermediate-2 and high risk according to IPSS [III, A] [16]. Splenectomy is generally not recommended in preparation for alloSCT [IV, D]. Pre-transplant JAK inhibitor treatment can reduce spleen size and improve constitutional symptoms, but is currently being tested in clinical studies and should be regarded as experimental [IV, D].

personalised medicine

MPNs are diseases that typically affect people within a mid-advanced age group. Therefore, any treatment decisions, especially regarding thrombosis prevention and selection of patients for alloSCT, should consider the patient's general condition and comorbidities. The diagnostic approach has improved remarkably with the discovery of recurrent phenotypic driver mutations, but there is still a need for standardised and validated mutational tests. The interpretation of BM histopathology features, as required by the current WHO classification, requires experienced pathologists, particularly for the differential diagnosis of early and/or for mutation-negative cases.

There are a number of prognostic scores that are useful for guiding treatment, yet they have been built on retrospective

series and are not validated prospectively, nor in the settings of conventional or new therapies. This is a challenge of particular relevance today, when novel targeted drugs are being used in clinical trials, and the first in-class JAK inhibitor has been approved. However, in spite of these recent advancements, we have to acknowledge that there are still too few effective treatment options for highly heterogeneous diseases such as MPNs, which additionally show high degrees of variability from patient to patient. In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

long-term follow-up and response evaluation

In patients with asymptomatic and well-controlled PV, follow-up visits can be scheduled at 2–4 month intervals to determine phlebotomy needs; in those with high-risk PV receiving stable HU dosage and/or IFN with very infrequent/absent phlebotomy needs, a 4- to 6-month interval may be appropriate. In low-risk ET patients, a visit at the 6- to 12-month interval is sufficient, while for those with high-risk ET receiving cytoreduction, a 3- to 4-month interval is recommended. Clinical and laboratory evaluation should be more frequent in the initial phases of disease management until a stable phlebotomy rate and/or drug dose is achieved.

Most patients maintain their HU dose steadily for several years, although in a minority of patients, excessive myelosuppression may develop that requires dose adjustment. Routine chemistry assessment (including at least lipid panel, glucose, renal and hepatic function tests) is recommend at 1-year intervals. While an ultrasound scan of the abdomen is suggested at first visits to exclude subclinical splanchnic vein thrombosis or spleen infarcts, assessment of splenomegaly can be conveniently carried out by palpation at each follow-up visit. Unless there is a suspicion of disease progression to post-PV/post-ET MF, there is no indication to

Table 6. Criteria for assessing response to treatment in polycythaemia vera (PV) and essential thrombocythaemia (ET) according to the ELN criteria [61]

	Criteria	
	PV	ET
Complete remission		
A	Durable resolution of disease-related signs including palpable haepatosplenomegaly, large symptom improvement AND	Durable resolution of disease-related signs including palpable haepatosplenomegaly, large symptom improvement AND
B	Durable peripheral blood count remission, defined as HCT lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9$/l, WBC count $<10 \times 10^9$/l, AND	Durable peripheral blood count remission, defined as platelet count $\leq 400 \times 10^9$/l, WBC count $<10 \times 10^9$/l, absence of leukoerythroblastosis, AND
C	Without progressive disease, and absence of any haemorrhagic or thrombotic events, AND	Without progressive disease, and absence of any haemorrhagic or thrombotic events, AND
D	Bone marrow histological remission defined as the presence of age-adjusted normal cellularity and disappearance of trilinear hyperplasia, and absence of >grade 1 reticulin fibrosis	Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis
Partial remission		
A	Durable resolution of disease-related signs including palpable haepatosplenomegaly, large symptom improvement AND	Durable resolution of disease-related signs including palpable haepatosplenomegaly, large symptom improvement AND
B	Durable peripheral blood count remission, defined as HCT lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9$/l, WBC count $<10 \times 10^9$/l, AND	Durable peripheral blood count remission, defined as platelet count $\leq 400 \times 10^9$/l, WBC count $<10 \times 10^9$/l, absence of leukoerythroblastosis, AND
C	Without progressive disease, and absence of any haemorrhagic or thrombotic events, AND	Without progressive disease, and absence of any haemorrhagic or thrombotic events, AND
D	Without bone marrow histological remission defined as persistence of trilinear hyperplasia	Without bone marrow histological remission defined as persistence of megakaryocyte hyperplasia
No response		
	Any response that does not satisfy partial remission	Any response that does not satisfy partial remission
Progressive disease		
	Transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukaemia	Transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukaemia

Durable = lasting at least 12 weeks.
Large symptom improvement = a ≥10-point decrease in the Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) [62].
Molecular response is not required for assignment as complete or partial response.
WBC, white blood cells; HCT, haematocrit; ELN, European LeukemiaNet.
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Table 7. Criteria for assessing response to treatment in PMF according to the IWG-MRT and ELN criteria [63]

Response categories	Required criteria (benefit must last >12 weeks to qualify as a response)
Complete remission (CR)	Bone marrow: age-adjusted normal cellularity; <5% blasts; ≤grade 1 fibrosis, *and* Peripheral blood: Hb ≥100 g/l, and <UNL; neutrophil count ≥1 × 10^9/l and <UNL; Platelets ≥100 × 10^9/l and <UNL; <2% immature myeloid cells, *and* Clinical: resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Partial remission (PR)	Peripheral blood: Hb ≥100 g/l, and <UNL; neutrophil count ≥1 × 10^9/l and <UNL; platelets ≥100 × 10^9/l and <UNL; <2% immature myeloid cells, *and* Clinical: resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH, *or* Bone marrow: age-adjusted normal cellularity; <5% blasts; <grade 1 fibrosis, and Peripheral blood: Hb ≥85 g/l but <100 g/l and <UNL; neutrophil count ≥1 × 10^9/l and <UNL; platelets ≥50 × 10^9/l but <100 × 10^9/l and <UNL; <2% immature myeloid cells, *and* Clinical: resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anaemia, spleen or symptom response without progressive disease or increase in severity of anaemia, thrombocytopaenia or neutropaenia
Anaemia response	Transfusion-independent patients: a >20 g/l increase in haemoglobin level Transfusion-dependent patients: becoming transfusion-independent
Spleen response	A baseline splenomegaly that is palpable at 5–10 cm below the LCM becomes not palpable, *or* A baseline splenomegaly that is palpable at >10 cm below the LCM decreases by ≥50% A baseline splenomegaly that is palpable at <5 cm below the LCM is not eligible for spleen response A spleen response requires confirmation by MRI or CT showing ≥35% spleen volume reduction
Symptom response	A ≥50% reduction in the MPN-SAF TSS
Progressive disease	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM, *or* A ≥100% increase in palpable distance below LCM for baseline splenomegaly 5–10 cm, *or* A 50% increase in palpable distance below LCM for baseline splenomegaly of >10 cm, *or* Leukaemic transformation confirmed by a bone marrow blast count of ≥20%, *or* A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10^9/l that last for at least 2 weeks
Stable disease	Belonging to none of the above response categories
Relapse	No longer meeting criteria for at least a CI after achieving CR, PR or CI, *or* Loss of anaemia response persisting for at least 1 month, *or* Loss of spleen response persisting for at least 1 month
Cytogenetic remission	At least 10 metaphases must be analysed for cytogenetic response evaluation and requires confirmation by repeat testing within a 6-month window CR: eradication of a pre-existing abnormality PR: ≥50% reduction in abnormal metaphases (PR applies only to patients with at least 10 abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analysed in peripheral blood granulocytes and requires confirmation by repeat testing within a 6-month window CR: eradication of a pre-existing abnormality PR: >50% decrease in allele burden (partial response applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

Grading of fibrosis is according to European scale (see Table 2).

Transfusion dependency before study enrolment is defined as transfusions of at least 6 units of packed red cells (PRBC), in the 12 weeks before study enrolment, for a haemoglobin level of <85 g/l, in the absence of bleeding or treatment-induced anaemia. In addition, the most recent transfusion episode must have occurred in the 28 days before study enrolment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive 'rolling' 12-week interval during the treatment phase, capped by a haemoglobin level of ≥85 g/l.

Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

MPN-SAF TSS, MPN symptom self-assessment form total symptom score. This is assessed by the patients themselves and includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss and fevers, which are ranked each from 0 (absent/as good as it can be) to 10 (worst imaginable/as worst as it can be); the TSS is the summation of all individual scores (0–100 scale).

PMF, primary myelofibrosis; IWG-MRT, International Working Group for Myeloproliferative Neoplasm Research and Treatment; ELN, European Leukemia Net; UNL, upper normal limit; EMH, extra-medullary haematopoiesis; LCM, left costal margin; MRI, magnetic resonance imaging; CT, computed tomography; Hb, haemoglobin.

serially repeat BM biopsy. Also, outside a clinical study and with the exception of patients IFNs, repeated assessment of mutation burden is not recommended. For patients with MF, visits must be more frequent, ranging from every week to 3 months depending on the general status, the presence of blood cell abnormalities and the type of therapy instituted. There is no firm evidence to suggest a specific type and/or frequency of follow-up; therefore, the above indications are mainly derived from experts' experience.

Criteria for assessing the response to treatment have been developed by the ELN and the IWG-MRT (Table 6). The criteria for PV and ET include definitions of complete and partial remission, incorporating clinical, haematological and histological response assessments, including a standardised symptom assessment form [61]. In the case of PMF, the revised criteria include six response categories encompassing clinical and haematological end points. Cytogenetic and molecular remissions, although considered, are not formally required for complete remission to be defined (Table 7) [63]. However, these criteria have been developed mainly for use in the clinical trials setting, and therefore should not be used as a tool to assess response to conventional therapies. In daily practice, the optimal but unvalidated target in ET include platelets $<400 \times 10^9$/l [V]. On the other hand, the randomised, controlled CYTO-PV trial established the superiority of an HCT <45% as the goal of treatment of patients with PV [I, A] [24].

special situations

antithrombotic therapy. The prophylactic use of low-dose aspirin in PV and ET has been already discussed. In patients with MF and normal/increased platelet counts, the use of low-dose aspirin is not

Table 8. European LeukemiaNet criteria for definition of resistance/intolerance to hydroxyurea in patients with polycythaemia vera, essential thrombocythaemia and primary myelofibrosis

(A) Polycythaemia vera [66]

1. Need for phlebotomy to keep HCT <45% after 3 months of at least 2 g/day of HU, OR
2. Uncontrolled myeloproliferation, i.e. platelet count $>400 \times 10^9$/l AND white blood cell count $>10 \times 10^9$/l after 3 months of at least 2 g/day of HU, OR
3. Failure to reduce massive[a] splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of HU, OR
4. Absolute neutrophil count $<1.0 \times 10^9$/l OR platelet count $<100 \times 10^9$/l OR Hb <100 g/l at the lowest dose of HU required to achieve a complete or partial clinicohaematological response, OR
5. Presence of leg ulcers or other unacceptable HU-related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU

(B) Essential thrombocythaemia [67]

- Platelet count $<600 \times 10^9$/l after 3 months of at least 2 g/day of HU (2.5 g/day in patients with a body weight >80 kg)
- Platelet count $<400 \times 10^9$/l and white blood cells <2500/μl at any dose of HU
- Platelet count $<400 \times 10^9$/l and Hb <10 g/dl at any dose of HU
- Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of HU
- HU-related fever

(C) Primary myelofibrosis [66]

1. Failure to: (i) reduce massive[a] or progressive[b] splenomegaly or haepatomegaly in splenectomised patients, by more than 50% as measured by palpation, OR (ii) completely relieve symptoms of splenomegaly or haepatomegaly in splenectomised patients, after 3 months of at least 2 g/day of HU
2. Uncontrolled myeloproliferation, i.e. platelet count $>400 \times 10^9$/l AND white blood cell count $>10 \times 10^9$/l after 3 months of at least 2 g/day of HU, OR
3. Failure to reduce massive[a] splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of HU, OR
4. Absolute neutrophil count $<1.0 \times 10^9$/l OR platelet count $<50 \times 10^9$/l at the lowest dose of HU required to achieve a complete or major clinicohaematological response, OR
5. Presence of leg ulcers or other unacceptable HU-related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU

[a]Organ extending by more than 10 cm from the costal margin.
[b]Organ increasing by more than 3 cm in the last 3 months.
For (A), complete response was defined as: HCT <45% without phlebotomy, platelet count $<400 \times 10^9$/l, white blood cell count $<10 \times 10^9$/l and no disease-related symptoms. Partial response was defined as: HCT <45% without phlebotomy, or response in three or more of the other criteria [68].
For (C), complete response was defined as a complete response in anaemia, splenomegaly and constitutional symptoms; major response was defined as any response in anaemia and splenomegaly without progression in constitutional symptoms, OR complete response in anaemia (or partial response in anaemia that was transfusion-dependent), and response in constitutional symptoms without progression in splenomegaly, OR any response in splenomegaly and response in constitutional symptoms without progression in anaemia [69].
HCT, haematocrit; Hb, haemoglobin; HU, hydroxyurea.

supported by clinical trials but may be appropriate considering a rate of thrombosis (fatal and non-fatal) of 1.75%, comparable with ET [64]. In patients who have already experienced major cardiovascular events, prevention of recurrence should be carried out according to general lines of management, depending on the type and site of previous thrombosis. In patients with splanchnic vein thrombosis or recurrent venous thrombosis and pulmonary embolism, lifelong oral anti-coagulation is usually suggested, although there is debate among experts in the absence of controlled studies [65]. The use of new anti-coagulants in these specific settings has not been evaluated yet. Indications for special situations are described below.

resistance or intolerance to first-line cytoreductive agents: The phenomenon of HU resistance or intolerance, as defined by the ELN (Table 8), is important. It identifies a group of ET or PV patients with a poor prognosis [70, 71], who require a change of treatment, and for whom novel therapies such as JAK inhibitors may be attractive. We recommend options for management that include (in the face of HU resistance or modest intolerance): reducing the dose by adjusting therapeutic targets (e.g. raising the platelet count target to 600×10^9/l) or switch therapy, usually to IFN (PV, ET) or anagrelide (ET). Busulfan may also be employed, preferably in older patients. It is important to consider that when HU is used with (or succeeded by) other agents, including busulfan, it will significantly increase the long-term risk of leukaemia [III, B]. Ruxolitinib has been approved for patients with PV who are refactory or resistant to HU [I, A] [34].

leukaemic transformation: Treatment of blast-phase MPN is usually disappointing [72]. Acute leukaemia-like regimens can be used in patients who are potential candidates for alloSCT [IV, B] [72, 73]. Benefits have been reported with azacitidine [IV, B] [74].

pregnancy: Current literature for pregnancy outcomes in MPN is sparse and likely to be subject to reporting bias. ET is the most common MPN in women of childbearing age. Maternal morbidity is uncommon in ET, but has been reported. Successful pregnancy occurs in up to 70% of patients. The literature regarding PV and MF, while very limited, is concordant with pregnancy outcome in ET. The suggested management of pregnancy in MPN derives mainly from a few single-centre studies [III, B] [75]. Disease management should be optimised before conception. HU and anagrelide should be stopped with an adequate wash-out period. If cytoreductive therapy is needed, IFN should be considered. Depending on the risk assessment results, women should be managed according to a standard-risk or high-risk pregnancy protocol, with multidisciplinary review. Unless contraindicated, all women should receive low-dose aspirin throughout pregnancy. For women with PV, venesection can be continued to maintain HCT levels within a gestation-appropriate target range, and is sufficient for standard-risk pregnancy. For high-risk pregnancy, i.e. if one (or more) of the factors in Table 9 is present or is likely to occur during pregnancy, additional treatment including cytoreductive therapy with IFN and low molecular weight heparin (LMWH) may be considered.

Foetal monitoring is suggested during pregnancy; scans should be carried out at 20, 26 and 34 weeks. Uterine artery Doppler should be carried out at 20 weeks. In the presence of a mean pulsatility index >1.4, the pregnancy may be considered high risk and treatment can be escalated, along with additional growth scans, as appropriate.

Table 9. Criteria for defining 'high risk' a pregnancy in the course of a myeloproliferative neoplasm (MPN) (adapted from [76])

- Sustained rise in platelet count rising to above 1500×10^9/l[a]
- Previous venous or arterial thrombosis
- Previous haemorrhage attributed to MPN[a]
- Previous pregnancy complication
  a. ≥1 unexplained deaths of a morphologically normal foetus ≥10 weeks of gestation
  b. ≥1 premature delivery of a morphologically normal foetus <34 weeks gestation because of:
     (i) Severe pre-eclampsia or eclampsia defined according to standard definitions
     (ii) Recognised features of placental insufficiency
  c. ≥3 unexplained consecutive miscarriages <10 weeks gestation, with maternal and paternal factors (anatomic, hormonal or chromosomal abnormalities) excluded
  d. Otherwise unexplained intra-uterine growth restriction
  e. Significant antepartum or postpartum haemorrhage requiring transfusion
- Abnormal uterine artery Doppler at 20 weeks (mean pulsatility index >1.4)

[a]Represents indication for IFN only rather than IFN plus low molecular weight heparin.

Local protocols with regard to interruption of LMWH should be adhered to during labour, and dehydration should be avoided. Postpartum LMWH thromboprophylaxis for 6 weeks should be considered. Thrombosis has been documented in the postpartum period, and blood counts should be monitored at this time.

Breastfeeding is safe with low-dose aspirin, heparin and warfarin (providing the new-born receives adequate vitamin K), but it is traditionally contraindicated with cytoreductive therapy. Decisions about breastfeeding while taking IFN should be made on an individual basis, after discussion regarding possible risks and benefits [III, B].

hormonal therapy: An individualised risk benefit assessment should be undertaken in considering hormonal therapy. The overall evidence grade is poor here [V]. For testosterone therapy, the major MPN-specific risk is of provoking an erythrocytosis which should be monitored. Concerning oestrogen and progesterone, the major risk is of thrombosis. In this case, topical therapies including coated intra-uterine devices are likely to be extremely low-risk and acceptable. For oral contraception, progesterone-only preparations are acceptable, but the combined oral contraceptive (i.e. both progesterone and oestrogen) is not recommended [V]. Where short-term hormonal manipulation is required, for example in fertility treatment, thromboprophylaxis should be considered and the patient should be counselled about thrombosis risk. Lastly, menopausal hormone replacement has recently been suggested to have minimal associated thrombosis

Table 10. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [78].

risk. An individual assessment weighing up the risks and need for treatment should be carried out.

surgery: Disease phenotype, individual patient variables and surgery-specific factors including choice of anaesthesia contribute to the personal risk of postoperative thrombosis and bleeding in MPN. Most of the data exist for ET patients, and arterial events are increased postoperatively at ~3.8%, but there is also a 10.5% bleeding risk with surgery [77]. This side-effect is thought to be caused by a combination of disease-related primary platelet abnormalities, anti-platelet agents and anti-coagulant therapy. For this reason, careful preoperative review is required, with consideration given to temporary control of platelet counts (especially for procedures where there is a significant risk if bleeding occurs or when patients are at increased risk of bleeding or thrombosis, as a consequence of the procedure). The use of anti-platelet and anti-coagulants should be adjusted according to local policy. Postoperative thromboprophylaxis with LMWH is recommended. It is not necessary to extend thromboprophylaxis beyond the normal period of time postoperatively simply because of an MPN diagnosis. Controlling blood counts preoperatively to standard targets for high-risk patients should be considered in MPN patients undergoing surgery, when bleeding is a risk or when thromboprophylaxis would normally be prescribed [IV, C].

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Table 10. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

AMV has reported advisory board or lecture honoraria from Novartis, lecture honoraria from Shire and institutional research support from Novartis. TB has reported advisory board and lecture honoraria from Novartis. FC has reported advisory board and honoraria from Novartis, Gilead, CTI/Baxter and AOP Orphan Pharmaceuticals, and lecture honoraria from Novartis and CTI/Baxter. CH has received advisory board or lecture honoraria from Novartis, CTI, YM Bioscience, Sanofi, Celgene, Gilead and Shire and institutional research support from Shire and Novartis. JJK has received advisory board or lecture honoraria from Novartis and Shire, and institutional research support from AOP Orphan Pharmaceuticals and Novartis. NK has reported advisory board and honoraria from Novartis and Sanofi, lecture honoraria from Novartis and Sanofi and institutional research support from Novartis and Sanofi. JT has reported consultant or advisory roles and honoraria from Novartis, Incyte Corporation, AOP Orphan Pharmaceuticals and Sanofi. CB has reported honoraria from Roche, Pfizer, Celgene, Pharmacyclics and Janssen and research grants from Roche and Janssen.

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