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REVIEW

Management of classical Philadelphia chromosome-negative myeloproliferative neoplasms in Asia: consensus of the Asian Myeloid Working Group

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Abstract
Myeloproliferative neoplasms (MPN) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized clinically by the proliferation of one or more hematopoietic lineage(s). The classical Philadelphia-chromosome (Ph)-negative MPNs include polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). The Asian Myeloid Working Group (AMWG) comprises representatives from fifteen Asian centers experienced in the management of MPN. This consensus from the AMWG aims to review the current evidence in the risk stratification and treatment of Ph-negative MPN, to identify management gaps for future improvement, and to offer pragmatic approaches for treatment commensurate with different levels of resources, drug availabilities and reimbursement policies in its constituent regions. The management of MPN should be patient-specific and based on accurate diagnostic and prognostic tools. In patients with PV, ET and early/prefibrotic PMF, symptoms and risk stratification will guide the need for early cytoreduction. In younger patients requiring cytoreduction and in those experiencing resistance or intolerance to hydroxyurea, recombinant interferon-α preparations (pegylated interferon-α 2A or ropeginterferon-α 2b) should be considered. In myelofibrosis, continuous risk assessment and symptom burden assessment are essential in guiding treatment selection. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) in MF should always be based on accurate risk stratification for disease-risk and post-HSCT outcome. Management of classical Ph-negative MPN entails accurate diagnosis, cytogenetic and molecular evaluation, risk stratification, and treatment strategies that are outcome-oriented (curative, disease modification, improvement of quality-of-life).

Keywords Myeloproliferative neoplasm · Asia · Treatment · Consensus · Guidelines

Background

Disease overview

Myeloproliferative neoplasms (MPN) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized clinically by the proliferation of one or more hematopoietic lineage(s) [1–3]. The classical Philadelphia-chromosome (Ph)-negative MPNs comprise polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) [1–5]. MF can also evolve from pre-existing PV or ET (SMF) [1, 6]. The most important driver mutations in Ph-negative MPNs are *JAK2*V617F (in > 95% of PV and 50–60% of ET/PMF), *JAK2* exon 12 mutations (in 3–5% of PV), *MPL* gene mutations (in 3–5% of ET and 5–10% of PMF), and *CALR* mutations (in ~25% of ET and PMF) [1, 3–5, 7–17]. MPNs without any of these driver mutations are referred to as "triple-negative" (TN), and constitute 10–20% cases of ET or PMF [1, 3, 4, 11, 15, 18–22]. A higher prevalence of *JAK2* exon 12 mutations was observed in Chinese PV patients [23, 24] and was associated with an earlier age of onset compared to those with *JAK2*V617F [24]. *MPL* mutations are less frequently observed in Asian patients with ET and PMF [22, 25–27]. A recent report from Taiwan showed that *MPL* mutations were observed in approximately 3% of ET and 4% of PMF [26, 28]. The prevalence of *CALR* mutations in ET and PMF in Japanese

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and Chinese patients was similar to that reported in Western populations [12, 13, 15, 17–19, 26, 29]. In Taiwan, *CALR* mutations were more frequently observed in overt PMF at approximately 31% [28]. TN cases were more frequently observed in ET patients in Taiwan at approximately 21% and less frequently observed in overt PMF [26, 28]. TN cases may harbor alternative gain-of-function mutations in *JAK2* or *MPL*, or mutations in non-driver genes, including but not limited to *ASXL1*, *EZH2*, *IDH1*/*IDH2*, *SF3B1*, *SRSF2* and *TET2* [1, 20, 21, 30–33]. Although non-driver gene mutations are detected in up to 50% of cases of MF, they are neither mutually exclusive nor disease-specific [33–35].

MPNs are initially indolent, and patients may or may not be symptomatic on presentation [5, 36–40]. Patients with PV typically present with symptoms of microvascular disturbances (headache, visual complaints, chest pain, erythromelalgia and distal paraesthesias), constitutional symptoms, "aquagenic" pruritus, fatigue, gout, palpable splenomegaly (36%), [5, 36, 41–51], thrombosis (15–16% arterial; 8–13% venous), or major hemorrhage [5, 37, 40–43, 51]. The disease develops through three phases: masked PV, overt polycythemic phase and the spent phase [52]. The serum erythropoietin (EPO) level is commonly suppressed but can be occasionally normal [53–56]. Post-phlebotomy serum EPO level was shown to be more specific in differentiating PV from secondary erythrocytosis [57]. ET is similar to PV in clinical presentation, but with lower incidences of splenomegaly (15–20%) and rarely hepatomegaly [5, 36, 40, 58, 59]. Approximately 30–50% of patients with PV or ET, especially younger individuals, may be asymptomatic with an incidental finding of blood count abnormalities [37, 38, 40, 58, 60]. PMF patients have variable clinical features, depending on the mutational profile and whether the disease is in the pre-fibrotic/early (pre-PMF) or overt fibrotic phases [1, 3, 5, 61]. Compared with pre-PMF, overt PMF is more commonly associated with anemia, leucoerythroblastosis, symptomatic disease, massive splenomegaly, and unfavorable karyotype [62]. The frequency of driver gene mutations is similar between pre-PMF and overt PMF. High mutation risk (HMR) mutations in *ASXL1*, *SRSF2*, *IDH1/2*, and *EZH2* are more frequently observed in overt PMF [62]. The median survival is significantly shorter in overt PMF compared with pre-PMF (7.2 vs. 17.6 years), with "triple negativity" for driver mutations and presence of HMR mutations being independent predictors of worse survivals [62]. Approximately 15% of patients with ET or PV progress to SMF over time, also referred to as post-ET or post-PV MF, with similar presentation and outcome as outcome as overt PMF [63].

Progression to secondary acute myeloid leukemia (sAML)/blast-phase is an important long-term complication in MPN. MF has the highest incidence of transformation (10–20%), followed by PV (3–7%) and ET (1–5%) [64–74].

Epidemiology, clinicopathologic features and outcome of Ph-negative MPNs in Asia

A multinational and multicenter registry "MERGE" had been established to determine the epidemiology of Ph-negative MPNs across sixteen Asian countries [37]. The results showed an incidence rate of 12–15 per 100,000 hospital patients, which was apparently higher than those observed in Western countries (3.1 per 100,000 and 2.7 per 100,000 in the United States and Europe respectively) [37, 75, 76]. ET was the most common subtype of MPN in Asian countries, followed by PV and MF, in contrast to PV being more common than ET and MF in Western populations [38, 77–80]. The incidence of MPN increases with age, peaking at 60–69 years [8, 38, 40, 71, 78–81]. ET shows a female predilection, whereas PV and MF were more common in men [17, 40, 77, 81]. On presentation, the symptom burden of patients was highest in MF (96% symptomatic), followed by PV and ET (92% symptomatic) [37]. In PV, a higher rate of thrombosis was observed in Thai people compared to international cohorts (29% vs 23.4%) [11, 40]. Cardiovascular comorbidities were also frequent (21% in ET, 20% in PV and 9% in MF) [37].

Survivals varied between different Asian populations, although these studies were limited by the sample size and their retrospective nature. In Korea, the 5-year overall survival (OS) was 97.7% for PV, 92.2% for ET and 53.1% for MF [78]. In Thailand, the 5-year OS was 91.7% for PV and 90.9% for ET [82]. In Hong Kong, the median OS of PMF and SMF was 5.5 years and 3.7 years [83]. In Taiwan, the 10-year OS for PMF was 73.6%, with median OS of 10.7 years and 5.9 years for early/prefibrotic and overt PMF [26, 28]. The 10-year OS for ET was 81.7% [26]. The overall time to disease progression was 14.1 months in the MERGE registry [37]. Outcome following progression to sAML was poor, with a median OS of 17 months in Singapore and 4 months in Hong Kong [83, 84].

Lack of treatment guidelines for MPN in Asian populations and need for developing a consensus

Various treatment guidelines for Ph-negative MPNs have been proposed by the British Society of Haematology, the European Leukemia Net (ELN), the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology, and the European Blood and Marrow Transplantation Group [34, 85–90]. In Asia, data on the clinicopathologic features, disease burden and outcome varied between studies [37]. The availability of diagnostic expertise and therapeutic choices are also heterogeneous among different populations [37, 78, 81, 91–95].

Improvement of the diagnosis, treatment and outcome of MPN in Asia requires as a first step a set of guidelines, which takes into account the specific clinical needs and resource limitations in different regions.

The Asian Myeloid Working Group and the MPN consensus process

The Asian Myeloid Working Group (AMWG) has been founded since 2016. In March 2021, it was registered as a formal legal entity. As of 2022, it comprised fifteen Asian centers. A consensus meeting MPN was convened in October 2019 in Singapore, where hematologists from constituent centers discussed the existing evidence for diagnosis and treatment of classical Ph-negative MPNs in Asia. Further discussions followed in the subsequent 2 years via virtual means, owing to travel restrictions arising from the COVID-19 pandemic. Literature review on the management of MPN was reviewed on MEDLINE database via PubMed database. A thorough literature review was continuously conducted to identify all English articles between 1 January 2010 and 31 January 2023. The key words related to MPN (PV, ET, PMF, post-PV MF and post-ET MF) were paired with the terms such as epidemiology, diagnosis, risk stratification, prognosis, treatment, hydroxyurea, anagrelide, interferon alfa, ruxolitinib, JAK inhibitors, and hematopoietic stem cell transplantation. A set of consensus recommendations was developed based on the available clinical evidence and the collective experience and expertise of the AMWG members, with the levels of healthcare resources and available treatment in different regions in Asia taken into full consideration. There were five iterations before the consensus statement was finalized. Only statements that were agreed by all members were included as consensus statements.

Management of Philadelphia chromosome negative classical MPNs: review of evidence and Amwg consensus

Diagnosis and initial investigations for PV, ET and MF

The diagnosis of MPN is based on the integration of clinical, molecular, and histopathological features, with histopathology playing a major role, supported by molecular genetics. Although each subtype of MPN has distinct presenting features, certain clinicopathologic features may overlap and lead to diagnostic uncertainties. Misdiagnoses have been reported, for instance between masked PV and ET, and between ET and pre-fibrotic PMF [1, 96–105]. Furthermore, MPNs may evolve or transform from one entity to another [1, 6, 15, 106].

The 2016 World Health Organization (WHO) classification is the most widely accepted diagnostic criteria for the major subtypes of MPN [1, 4, 34, 107–109]. The classification is useful in assisting clinical research and registry establishment as it provides a standard for patient categorization, ensuring data accuracy and allowing further investigation of different subtypes to be performed [4, 17]. For post-PV and post-ET MF, the International Working Group—Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) diagnostic criteria are widely accepted [110]. In the latest revision of the WHO Classification in 2022 and the International Consensus Classification (ICC) of myeloid malignancies [2, 111, 112], the main categories of Ph-negative MPN and their pathologic features remain similar, with further emphasis on the correlation between clinicopathologic and molecular features in making a diagnosis.

AMWG Consensus on the diagnosis and initial investigations of PV, ET and PMF

- The aims of initial investigations in MPN are to accurately diagnose, risk stratify, and evaluate disease-related complications (Table 1).
- The WHO classification should be employed in the diagnosis of Ph-negative MPN.
- The diagnosis of MPN requires careful bone marrow morphologic assessment and correlation with hematologic, cytogenetic and molecular features (supplementary tables 1–3).
- Assessment of driver gene mutations in *JAK2*, *CALR* and *MPL* are essential in the diagnosis of MPN.
- Assessment of additional mutations in patients with "triple negative MPN" may have a role in demonstrating clonality.
- Baseline symptom burden should be assessed using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS).
- In MF patients who are potential candidates for allogeneic hematopoietic stem cell transplantation (allo-HSCT) (age < 65 years with good performance status), human leukocyte antigen (HLA) typing should be performed.

Risk stratification in MPN

Risk stratification in PV

The main objective is to determine the risk of thrombosis (supplementary table 4). Conventionally, a two-tier system is adopted for risk stratification, where patients ≥ 60 years old and/or with a history of thrombosis are classified as high risk, while those < 60 years old with no thrombotic events

Table 1 AMWG recommendations for the initial assessment and investigations in Ph-negative myeloproliferative neoplasms

History and physical examination Assessment of prior or current thrombotic and hemorrhagic events Assessment of cardiovascular risk factors Medical history, psychiatric history, transfusion history Exclusion of reactive causes of thrombocytosis or leucocytosis Assessment of hepatosplenomegaly
CBC with differential count and blood film review
Serum electrolytes, RFT, LFT, LDH, urate
Serum EPO level for polycythemia
Iron profile
Clotting profile in patients with thrombocytosis
vWF assays (for the exclusion of acquired vWD in patients with thrombocytosis or bleeding tendency)
Hepatitis B serology including HBsAg/Ab and anti-HBc IgG
HBV DNA in patients who are HBsAg or anti-HBc IgG positive
Hepatitis C serology
Thyroid function tests in candidates for IFN-α
Autoimmune markers (e.g. ANA and RF) and inflammatory markers (e.g. ESR and CRP) in the appropriate
CXR
Exclusion of active or latent tuberculosis in candidates for ruxolitinib
Other investigations to exclude reactive causes guided by medical history and physical examination
Bone marrow aspirate and trephine biopsy for morphologic assessment, reticulin staining and trichrome staining
Karyotype
*JAK2*V617F assessment
JAK2 exon 12 assessment in PV negative for *JAK2V617F*
CALR and *MPL* assessment in ET and PMF negative for *JAK2*V617F
RT-PCR or FISH for *BCR::ABL1* to exclude CML in MPN negative for *JAK2/CALR/MPL* mutations
NGS for myeloid gene panel For risk stratification in all patients with PMF or SMF who are potential candidates for allo-HSCT To establish clonality in patients with MPN who are negative for *JAK2/CALR/MPL* mutations
Assessment of symptom burden using MPN-SAF
HLA typing in patients with PMF and SMF who are potential candidates for allo-HSCT

CBC: complete blood count; RFT: renal function test; LFT: liver function test; LDH: lactate dehydrogenase; EPO: erythropoietin; vWF: von Willebrand Factor; vWD: von Willebrand disease; HBsAg/Ab: hepatitis B surface antigen/antibody; anti-HBc IgG: anti-hepatitis B core IgG: ANA: anti-nuclear antibodies; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CXR: chest X-ray; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis; SMF: secondary myelofibrosis; CML: chronic myeloid leukemia; RT-PCR: reverse transcription-polymerase chain reaction; FISH: fluorescence in-situ hybridization; allo-HSCT: allogeneic hematopoietic stem cell transplantation

are classified as low risk. This model is recommended by both the NCCN and ELN guidelines [34, 113]. Apart from age and history of thrombosis, additional risk factors for thrombosis can be identified. In the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) study, age > 65 years and a history of thrombosis were most predictive of subsequent thromboembolic events. Other risk factors identified in this study included hypertension, smoking, congestive heart failure, and a leukocyte count $> 15 \times 10^9$/L [114, 115]. In the Cytoreductive therapy in PV (CYTO-PV) study, leukocyte count $> 11 \times 10^9$/L was associated with an increased risk of thrombosis [116]. The IWG-MRT study showed differences between risk factors of arterial and venous events. The risk of arterial thrombosis was shown to be increased by a history of arterial thrombosis and hypertension, whereas the risk of venous thromboembolism was increased by age ≥ 65 years and a history of venous thrombosis [101].

Risk stratification in ET

Similar to PV, conventional risk stratification in ET categorizes patients into high risk and low risk according to their age (> 60 vs. ≤ 60 years) and previous thrombotic event [117–119]. Recently, this stratification model has been replaced by the International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis), which classifies patients into three risk

groups (high risk, intermediate risk, and low risk) based on age (> 60 vs. ≤ 60 years), history of thrombosis, cardiovascular risk factors (hypertension, diabetes mellitus, and smoking), and *JAK2*V617F status (supplementary table 5). Further studies have validated the IPSET-thrombosis score and demonstrated that it was superior to conventional models in predicting thrombotic events [117–119]. A four-tier revised IPSET-thrombosis score has also been proposed (supplementary table 6) [118, 119]. The NCCN and ELN guidelines recommend the use of the three-tier IPSET-thrombosis score or the four-tier revised IPSET-thrombosis score for risk stratification in ET [34, 113].

Risk stratification in MF

Conventional prognostic models for prediction of survivals stratify patients based on their clinical and hematological features (supplementary table 7). The four-tier International Prognostic Scoring System (IPSS) applied at disease presentation used to be most widely employed [120]. The Dynamic IPSS (DIPSS) allows risk stratification during the course of disease and is also widely adopted [121]. The identification of cytogenetic risk factors affecting prognosis has resulted in the development of DIPSS-plus [8, 122–126]. The ELN guideline recommends the use of IPSS for all patients with PMF at diagnosis and DIPSS and DIPSS-plus for reassessment during the course of disease [34]. The NCCN guidelines recommend the use of DIPSS and DIPSS-plus for all patients with PMF [113]. The Genetically Inspired Prognostic Scoring System (GIPSS) is a more objective prognostic model that includes revised cytogenetic and molecular risk factors (supplementary tables 8 and 9) [127]. To evaluate patients who are potential candidates for allo-HSCT, three other prognostic systems have been developed. Mutation-enhanced IPSS for patients aged ≤ 70 years (MIPSS70) stratifies them based on clinical, hematological and genetic factors. The key genetic factors associated with adverse outcomes include the absence of type 1 *CALR* mutation status and the presence of HMR mutations. The MIPSS70 plus (MIPSS70 +) and MIPSS70 + version 2.0 (MIPSS70 + v2.0) take into account both cytogenetic and molecular risk factors (supplementary tables 10–12) [128, 129]. MIPSS70 and MIPSS70 + v2.0 are recommended by the NCCN guidelines when allo-HSCT is considered [113]. In SMF, the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) has been developed (supplementary table 13). MYSEC-PM is superior to conventional IPSS in predicting survivals in SMF [130] and is recommended by the NCCN guidelines [113].

AMWG consensus for risk stratification of PV, ET and MF

- In PV, age > 60 years and prior history of thrombosis are the key risk factors for thrombotic events.
- In ET, the three-tier IPSET-thrombosis score and cardiovascular risk factors are recommended for predicting the risk of thrombotic events.
- In resource-limited centers where molecular studies may not be routinely performed in patients with PMF or SMF, the DIPSS or DIPSS-plus are recommended.
- When cytogenetic studies and myeloid gene panel NGS are available, the MIPSS70 + v2.0 is recommended for management decisions, especially in patients eligible for allo-HSCT.
- In SMF, the MYSEC-PM prognostic model may be used.

Treatment of PV

Treatment of PV includes anti-platelet therapy with aspirin and hematocrit control (aiming at < 0.45) with phlebotomy, and cytoreduction as indicated. The use of anti-platelet therapy was shown to be effective and safe in the ECLAP study [131]. Phlebotomy or hydroxyurea (HU or hydroxycarbamide) was shown to be effective in reducing the rates of cardiovascular death and major thrombotic events in the CTYO-PV study when the hematocrit target of < 0.45 was maintained [99]. A lower hematocrit target of < 0.42 may be considered in women experiencing progressive symptoms [85, 113, 132]. Various guidelines recommend the use of low-dose aspirin for managing vascular events and phlebotomy for maintaining the hematocrit levels at < 0.45 [34, 113, 133–135]. Initial treatment of low-risk PV (age < 60 without prior history of thrombosis) does not include routine cytoreduction [113, 136]. However, in this population, cytoreduction is recommended if they fulfill one or more of the following criteria: strictly defined intolerance to phlebotomy, symptomatic progressive splenomegaly, persistent leukocytosis > 15×10^9/L, progressive leukocytosis (≥ 100% increase if baseline leukocyte count is < 10×10^9/L or ≥ 50% increase if baseline leukocyte count is > 10×10^9/L), extreme thrombocytosis (platelet count > 1500×10^9/L), inadequate hematocrit control requiring phlebotomies, persistently high cardiovascular risk and persistently high symptoms burden (e.g. total symptom score ≥ 20 or pruritus score ≥ 5) [137]. Initial treatment of patients with high-risk PV includes cytoreduction in addition to aspirin and phlebotomy.

HU and recombinant interferon alpha (IFNα) preparations such as pegylated IFNα 2a (peg-IFNα 2a) or ropeginterferon alfa 2b (ropeg-IFNα-2b) are the most commonly used cytoreductive agents [34, 138, 139]. HU, ribonucleotide reductase inhibitor [140, 141], is an antimetabolite that is potentially leukemogenic [142]. Approximately 15–24%

of patients on HU develop resistance or intolerance [143]. Cutaneous ulceration is seen in HU-intolerant patients and a common cause of drug interruption or cessation [144]. IFNα should be considered in young patients, women of child-bearing age, and during pregnancy if cytoreduction is required. IFNα induces hematologic responses in the majority of patient and may lead to molecular responses in some patients [145]. Side-effects of IFNα include flu-like symptoms, fever, malaise, nausea, vomiting, alopecia, autoimmune disorders, thyroid dysfunction, cytopenias and neuropsychiatric problems [144, 146]. IFNα is contraindicated in patients with autoimmune disorders, uncontrolled hepatitis, thyrotoxicosis, psychiatric disorders (depression), and epileptic disorders [147–149]. Peg-IFNα-2a and ropeg-IFNα-2b are better tolerated [139, 146]. Ropeg-IFNα-2b [139, 150] is approved by the EMA and the US-FDA for use as a second-line agent in cases resistant or intolerant to HU. In patients with low-risk PV requiring cytoreduction, Ropeg-IFNα-2b or Peg-IFNα-2a are the recommended options.

Ruxolitinib, a non-selective JAK1/JAK2 tyrosine kinase inhibitor, is an alternative for patients intolerant or resistant to HU (supplementary table 14) [151, 152]. In patients with PV resistant or intolerant to HU, ruxolitinib achieved complete hematologic responses in 23–24% of cases [153, 154]. Responses were durable with 70% of patients maintaining remission for ≥ 80 weeks [155]. Ruxolitinib was approved by the United States Food and Drug Administration (US-FDA) and the European Medicine Agency (EMA) in 2014 and 2015 for patients resistant or intolerant to HU [34, 156, 157]. Busulfan, an alkylating agent, may be considered in older individuals who are refractory to HU [158–160]. However, it significantly increases the risk of sAML and other malignancies, so that its use is not recommended [85]. The monitoring of cardiovascular risk factors (smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia) [90], and the occurrence of new thrombo-hemorrhagic events, is advised along with appropriate management [113].

AMWG consensus on the treatment of PV (Fig. 1A)

- The standard treatment of PV generally includes aspirin and phlebotomy.
- A hematocrit of < 0.45 should be maintained.
- Decision for cytoreduction is primarily driven by conventional risk factors (age and prior thrombosis). HU and recombinant IFNα preparations are the most common first-line options for cytoreduction.
- Recombinant IFNα are the first-line treatment options for women of child-bearing age or younger patients (age < 70 years). Peg-IFNα-2a or ropeg-IFNα-2b are preferred due to their extended half-life, which allows less frequent administration with better tolerability [146, 161, 162].
- In case of resistance or intolerance to HU, change of therapy is recommended. The definition of HU resistance according to the ELN consensus (use of HU at ≥ 2 g/day for ≥ 3 months)[163] may not be applicable to Asian patients, as most of them develop intolerance to HU at lower doses. In this setting, peg-IFNα-2a or ropeg-IFNα-2b should be considered if available.
- Ruxolitinib is another second-line option for patients with resistance/intolerance to frontline HU.
- In low-risk PV, cytoreduction is recommended if they fulfill one or more of the following criteria: strictly

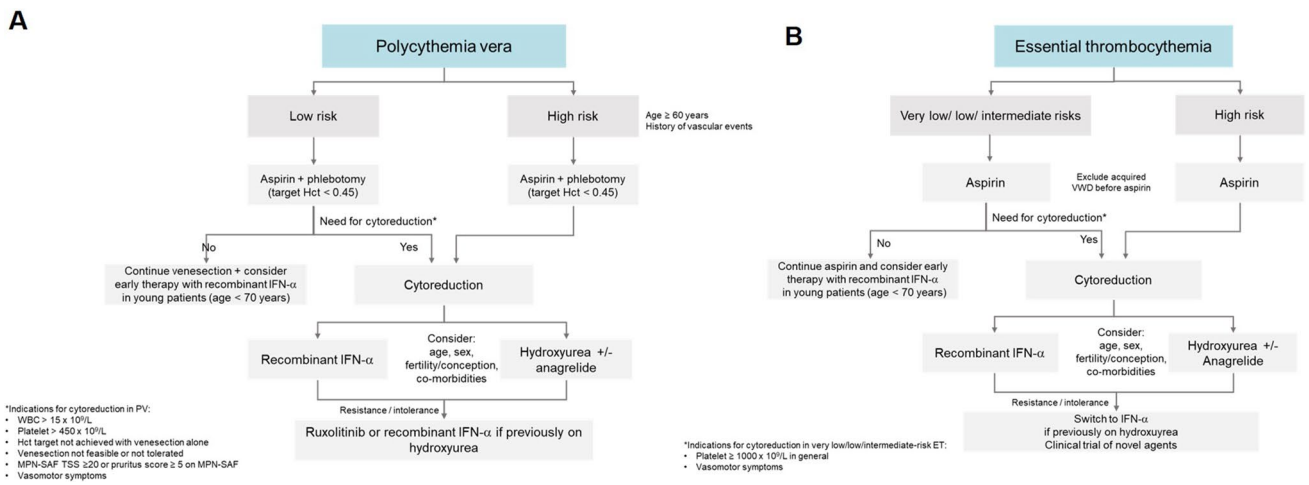

Fig. 1 A AMWG proposed treatment algorithm for polycythemia vera; B AMWG proposed treatment algorithm for essential thrombocythemia. AMWG: Asian Myeloid Working Group; Hct: hematocrit; IFN-α: interferon alfa; WBC: white blood cell; MPN-SAF: Myeloproliferative Neoplasm-Symptom Assessment Form; TSS: Total Symptom Score; ±: with or without; VWD: von Willebrand disease; PV: polycythemia vera; ET: essential thromobocythemia

defined intolerance to phlebotomy, symptomatic progressive splenomegaly, persistent leukocytosis > 15×10^9/L, progressive leukocytosis (≥ 100% increase if baseline leukocyte count is < 10×10^9/L or ≥ 50% increase if baseline leukocyte count is > 10×10^9/L), extreme thrombocytosis (platelet count > 1500×10^9/L), inadequate hematocrit control requiring phlebotomies, persistently high cardiovascular risk and persistently high symptoms burden[137]. In high-risk PV, cytoreduction is required in all patients.
- The aim of cytoreduction is to maintain hematocrit at < 0.45, platelet count at ≤ 450×10^9/L and leukocyte count at ≤ 15×10^9/L.

Treatment of ET

The use of low-dose aspirin generally recommended for the prevention of thrombotic events except in asymptomatic patients with low-risk *CALR*-mutated ET [164]. Cytoreduction is considered based on patient and disease factors. Cytoreductive agents used are similar to those in PV, including HU, IFNα and anagrelide. Anagrelide, an oral imidazoquinazoline derivative [165], inhibits megakaryocytic maturation in the post-mitotic phase [166, 167]. It effectively lowers platelet count and reduces platelet aggregation [167, 168]. Anagrelide is approved by the EMA for use in patients resistant or intolerant to HU [169]. In Japan [170] and the US [171], it is also licensed for first-line treatment. Risk of sAML and possibly other cancers in patients on HU may be one of the factors favoring the use of anagrelide. In a large-scale post-marketing observational investigation in 3649 patients with high-risk ET, a higher standardized incidence ratio of sAML was found in patients on HU, whereas no cases of AML occurred in patients treated with anagrelide [172, 173]. The non-inferiority of anagrelide to HU in preventing thrombotic complications was established in a phase 3 trial [174]. The inhibitory activity of anagrelide on phosphodiesterase III contributes to the cardiovascular adverse events such as palpitations and tachycardia [165]. It is also associated with a higher incidence of SMF transformation than HU [169, 175–177].

Current guidelines generally advise observation for very low-risk, low-risk and intermediate-risk patients. Aspirin should be administered to patients with microvascular disturbances [105]. In patients with thrombocytosis and acquired von Willebrand disease (vWD), cytoreduction may be required to reduce the risk of bleeding prior to aspirin use [166].

All patients with high-risk ET should receive cytoreduction in addition to aspirin. The NCCN guideline recommends the concomitant use of HU or anagrelide with aspirin as initial treatment. On the contrary, the ELN guideline suggests the use of anagrelide as a second-line agent only when patients are not responding to HU [34, 105].

AMWG consensus on the treatment of ET (Fig. 1B)

- Anti-platelet therapy is generally commended unless contraindicated.
- Aspirin is usually the drug of choice, with clopidogrel used in patients allergic or intolerant to aspirin [178].
- Anti-platelet agents should be deferred in patients with extreme thrombocytosis (platelet count > 1500×10^9/L) due to increased risks of bleeding in view of the development of acquired vWD [166, 178].
- Cytoreduction should be initiated taking into account the presenting symptoms and the risk category. We recommend cytoreduction in relatively asymptomatic very low-risk and low-risk patients with platelet counts ≥ 1000–1500×10^9/L.
- Cytoreduction is required in all intermediate- and high-risk patients.
- Options of cytoreduction include HU, Peg-IFNα-2A or anagrelide.
- Recombinant IFNα preparations should be used as first-line treatment for younger patients (age < 70 years) and in women of child-bearing age, due to the potential leukemogenicity and teratogenicity of HU. In older patients or those with contraindications to IFNα, HU is recommended.
- Upfront or single-agent use of anagrelide is generally reserved for patients with intolerance or contraindications to HU or IFNα.
- Ruxolitinib has not demonstrated superior clinicohematologic responses to HU and is therefore not routinely recommended [25, 179].
- Patients should be monitored regularly for treatment response, thrombotic events and disease-related bleeding as a result of platelet dysfunction or acquired vWD. Cardiovascular risk factors should be appropriately evaluated and managed.

Treatment of MF

Major goals of treatment in MF include symptom control, spleen size reduction, improving quality-of-life and OS [113, 180]. The therapeutic approach is based on risk stratification, symptomatology and individualized clinical needs [34, 105, 113]. Assessment of symptom burden by MPN-SAF or the Myelofibrosis Symptom Assessment Form (MF-SAF) is generally recommended [113]. These symptom assessment tools are performed on presentation and during the course of treatment, for quantification of common problems including fatigue, poor concentration, early satiety, inactivity, pruritus, bone pain, abdominal discomfort, fever, weight loss

and night sweats [47, 113]. Anemia is a major problem in MF. Alternative causes of anemia should be excluded [113, 181–183]. Current guidelines recommend the use of ESAs as first-line treatment in anemic patients with low serum EPO levels [113, 181, 184, 185]. Danazol is an acceptable alternative [87, 113, 181, 184, 185]. Thalidomide in combination with corticosteroid should be considered in patients not responding to ESAs or danazol [34, 181, 185]. Other immunomodulatory drugs such as lenalidomide or pomalidomide are generally not recommended, due to the risk of progressive cytopenia [34, 87, 113].

Observation alone is suggested for both low or intermediate-1 risk patients without significant symptoms [34]. Ruxolitinib is used as first-line treatment for intermediate-2 and high IPSS/ DIPSS/ DIPSS-plus risks [34, 186]. In the COMFORT-I study, spleen volume reduction ≥ 35% (SVR35) and total symptom score reduction ≥ 50% (TSS50) was achieved in 42% and 46% of patients with intermediate-2 or high-risk MF at Week 24 [187]. In the COMFORT-II study, 32% of patients with intermediate-2 or high-risk MF achieved SVR35 at Week 48 [188]. The median duration of SVR35 was approximately 3.2 years with maintenance ruxolitinib in both the COMFORT-I and COMFORT-II studies [189, 190]. In the EXPAND study that evaluated patients with platelet count ranging from 50 to 100×10^9/L, the use of ruxolitinib at 10 mg twice per day demonstrated clinically meaningful improvement in spleen size and symptoms. Pooled analysis and long-term follow-up of the COMFORT-I and COMFORT-II studies showed significant prolongation of overall survival (OS) compared to the control groups [191]. The OS benefit of ruxolitinib was also shown in large retrospective studies [192, 193]. The ERNEST study which evaluated the outcome of 1010 patients with MF in 5 European countries showed a significantly better OS with the use of Ruxolitinib compared to hydroxyurea [193]. The timing of initiation of ruxolitinib has been shown to impact on the clinical benefits. Patients who receive ruxolitinib ≤ 12 months from the diagnosis of MF had better spleen responses, longer OS and fewer hematologic toxicities [191]. Nevertheless, data demonstrating survival benefit of ruxolitinib is heterogeneous and inconsistent across different studies and requires further validation in large prospective studies. Patients with lower risk MF may also benefit from treatment with ruxolitinib treatment [194, 195]. The phase II ROBUST trial showed that 50% and 21% of patients with intermediate-1-risk MF achieved ≥ 50% reduction in spleen length and ≥ 50% reduction in MFSAF TSS respectively at Week 48 [194]. The phase 3b JUMP study showed that 61% of patients with intermediate-1-risk MF achieved ≥ 50% reduction in spleen length at Week 48 [195]. In the COMFORT-I study, the mean reduction of *JAK2*V617F allele burden was 21.5% at Week 48 [187, 189]. In the COMFORT-II study, durable reduction in *JAK2*V617F allele burden > 20% from baseline was achieved in one-third of patients at Week 168 and 192 [190]. In the COMFORT-II study, 15.8% and 32.2% of patients randomized to ruxolitinib had improved and stable bone marrow fibrosis respectively [189]. Both the COMFORT-I and COMFORT-II studies showed that patients on ruxolitinib has reduced plasma C-reactive protein, interleukin (IL)-6 and tumor necrosis factor (TNF)-α and increased levels of leptin and erythropoietin [187]. Approximately 50% of patients discontinue ruxolitinib after 3 years, mostly due to disease progression, suboptimal response or cytopenia [196–198]. Definitions of "ruxolitinib failure" vary. [199–201] Definitions are largely based on studies evaluating JAK inhibitors in the second line setting and generally refers disease progression to accelerated or blast phase, suboptimal response of spleen or constitutional symptoms, worsening splenomegaly or constitutional symptoms after initial response, and the development of transfusion-dependent anemia or grade 3/4 thrombocytopenia, anemia of hemorrhagic events while on ruxolitinib [196, 200–203]. Outcome after ruxolitinib discontinuation is generally poor with a median OS of approximately 14 months after discontinuation [64, 204, 205]. Patients with ≥ 3 non-driver gene mutations generally have a shorter time-to-discontinuation [206]. The reason for treatment failure must be accurately defined. Anemia and thrombocytopenia that can be managed by dose modifications, transient interruption or additional supportive measures should not prompt permanent ruxolitinib discontinuation and most patients still derive clinical benefits in such circumstances. In most patients, the nadir for anemia and thrombocytopenia is within 8–12 weeks from initiation [187–189]. Thereafter, hemoglobin levels usually return to baseline and platelet levels return to a new steady-state [187–189]. Herpes zoster reactivation, viral hepatitis B reactivation and other opportunistic infections have been reported in patients on ruxolitinib [189, 195, 207]. The ruxolitinib is also highly relevant in the era of COVID-19. Patients with MF have adverse outcomes following COVID-19. Abrupt ruxolitinib discontinuation in patients with severe COVID-19 is also associated with worse survivals. Patients on ruxolitinib may also show attenuated immune responses to COVID-19 vaccinations [208].

The association between second primary cancers such as B-cell lymphomas and non melanomatous skin cancers in ruxolitinib-treated patients remains controversial [189, 190, 209]. The risk of infections and second malignancies may reflect the patient population, the disease itself and prior therapy such as hydroxyurea. The ruxolitinib is also highly relevant in the era of COVID-19. Patients with MF have adverse outcomes following COVID-19. Abrupt ruxolitinib discontinuation in patients with severe COVID-19 is also associated with worse survivals. Patients on ruxolitinib may also show attenuated immune responses COVID-19 vaccinations [208].

Fedratinib is a potent JAK2/ fms-like tyrosine kinase 3 (FLT3) inhibitor approved by the FDA and EMA for patients with intermediate-2 and high-risk MF patients regardless of prior ruxolitinib use [198, 210]. Fedratinib exerts off-target inhibitory effect against FLT3 and bromodomain 4 (BRD4) [211]. BRD4 is a member of the BET protein family that enhances pro-inflammatory NF-κB to increase the release of pro-inflammatory cytokines. Combined inhibition of the JAK/STAT pathway and BRD4 synergistically suppresses NF-κB hyperactivation and cytokine production [211–213]. Fedratinib effectively reduces splenomegaly and symptom burden in both JAK inhibitor-naïve and JAK inhibitor-treated patients in the JAKARTA-2 and JAKARTA-3 studies [202, 214–217]. In JAK inhibitor naïve patients, SVR35 and TSS50 was achieved in 36% and 36% of patients treated with Fedratinib at 400 mg daily at Week 24 respectively [216, 217]. Fedratinib-treated patients also achieve clinically meaningful improvement in health-related QOL [218]. Control of cytokine-mediated symptom complex and disease manifestations appear to be a distinct advantage of fedratinib.

Pacritinib is a JAK2/FLT3 inhibitor approved by the US FDA for intermediate-2 or high-risk MF with platelet count $\leq 50 \times 10^9$/L [219]. Its off-target inhibitory action against interleukin-1 receptor-associated kinase 1 (IRAK1) and colony-stimulating factor 1 receptor (CSF1R) [219–224] promotes rapid suppression of inflammatory pathways resulting in early improvement in cytokine-mediated symptom complex [225]. With minimal JAK1 inhibition, pacritinib is less myelosuppressive and immunosuppressive [221, 222, 224, 225]. These properties may offer a distinct advantage in patients with a cytopenic or myelodepletive phenotype [224, 226, 227]. In the PERSIST-1 and PERSIST-2 studies, SVR35 and TSS50 was 19% and 19%; and 18% and 25% at Week 24 respectively [219, 228].

Momelotinib is a JAK1/JAK2 inhibitor that has additional inhibitory effect against activin A receptor type I (ACVR1) [229–232]. ACVR1 is an important mediator of SMAD2/3 signalling that upregulates hepcidin production and results in iron-restricted erythropoiesis. SMAD2/3 signalling is particularly implicated in the inhibition of terminal erythroid maturation and ineffective erythropoiesis [233]. Improved red-cell transfusion dependence and SVR were observed in MF patients in the phase 3 SIMPLIFY studies [230, 234–236]. In the SIMPLIFY-1 study [235], the only study with head-to-head comparison between momelotinib and ruxolitinib, the rate of SVR35 was similar between the two arms at Week 24 (momelotinib: 26.5%; ruxolitinib: 29%) while symptom score reduction at Week 24 was higher in the ruxolitinib arm (momelotinib: 28.4%; ruxolitinib 42.2%). The rate of red cell transfusion independence at Week 24 was remarkably different (momelotinib: 66.5%; ruxolitinib 49.3%) [235]. Achievement of transfusion-independence with momelotinib was associated with superior 3-year OS at 77.2% versus 51.6% [235, 237]. In the SIMPLIFY-2 study, momelotinib was evaluated in patients with suboptimal response or intolerance to ruxolitinib [236]. At Week 24, SVR35 was achieved in 7% in the momelotinib arm versus 6% in patients on the best available therapy (BAT) arm that comprised ruxolitinib in 89% of patients [236]. Transfusion independence was achieved in 49.3% in the momelotinib arm and 21% in the BAT arm [236]. The phase 3 MOMENTUM study [238] evaluated JAK inhibitor-exposed patients with intermediate or high-risk MF with hemoglobin < 10 g/dL, symptom score ≥ 10 and platelet $\geq 25 \times 10^9$/L. SVR35 and symptoms score response rates at Week 24 were respectively achieved in 23% and 24.6% in the momelotinib arm and 3% and 9.2% respectively in the danazol arm [238]. The rates of transfusion independence at Week 24 was 31% for momelotinib and 20% for danazol [238]. Momelotinib was pending approval by the FDA for the treatment of MF at the time of writing of this manuscript.

AMWG consensus for the treatment of MF

- Ruxolitinib is considered the first-line treatment for IPSS intermediate-2 / high risk disease and symptomatic splenomegaly. Its use prior to allo-HSCT may also improve performance status and control splenomegaly.
- Reduction of spleen size and symptom burden are two key treatment goals (Figs. 2A-C).
- In patients with anemia, treatment with transfusion, thalidomide with or without prednisolone, or erythropoietin-stimulating agent (ESA) is preferred over lowering the dosage of ruxolitinib, which may compromise symptom and spleen responses [201]. Stabilization of anemia is usually seen within 3–6 months of ruxolitinib treatment [239]. If anemia persists beyond 6 months, alternative causes should be considered before ruxolitinib dose titration. Dose modifications may also be necessary in patients experiencing non-hematologic toxicities.
- A well-organized, comprehensive transfusion program is essential in transfusion-dependent patients.
- Iron overload and its complications should be prevented with early iron chelation. Balancing cost and patient compliance, oral deferiprone is preferred over subcutaneous or intravenous deferoxamine. For patients not tolerating deferiprone or deferoxamine, deferasirox may be considered.
- Ruxolitinib dose adjustments is required in patients with renal impairment and liver function derangement. In addition, drug-drug interactions should be noted [240]. Dosage of ruxolitinib has to be reduced by 50% with concomitant use of CYP3A4 inhibitors (e.g. triazoles, macrolides, ritonavir, verapamil), whilst reduced

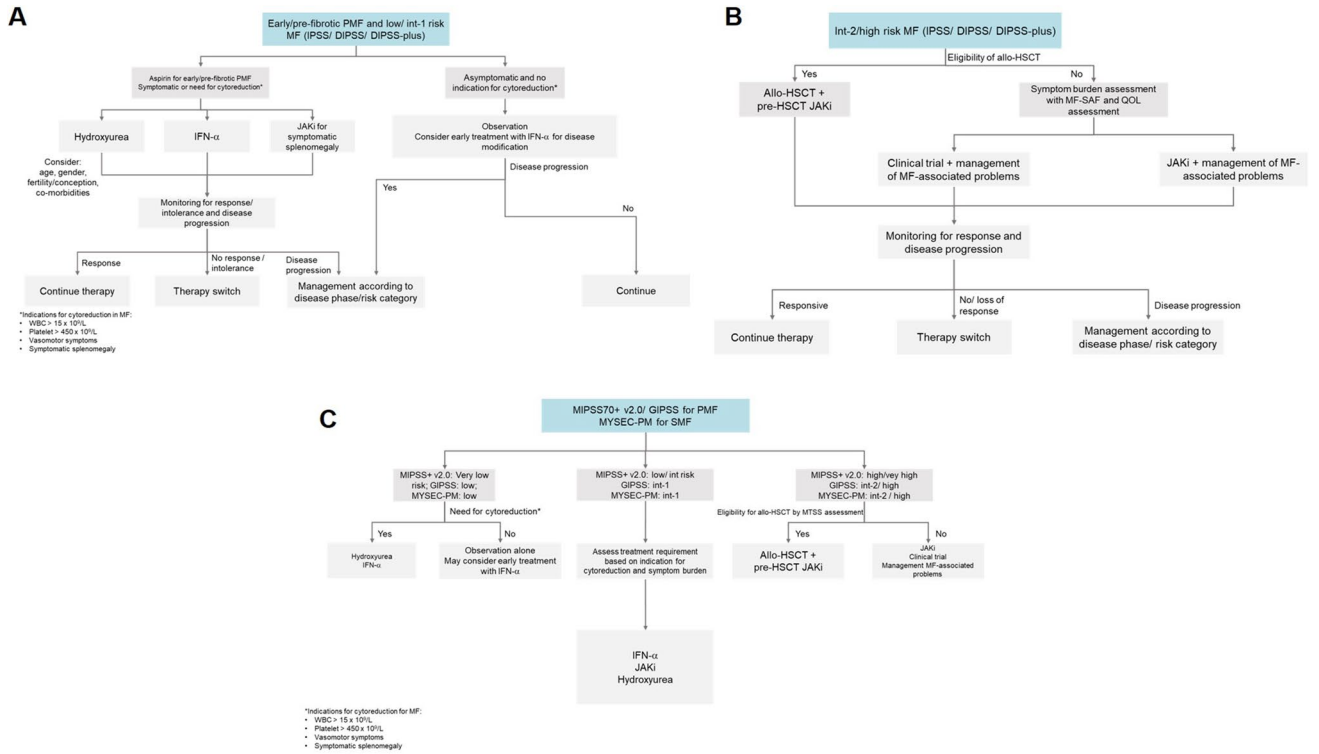

Fig. 2 **A** AMWG proposed treatment algorithm for early/pre-fibrotic PMF and low/int-1 risk MF based on IPSS/DIPSS/DIPSS-plus; **B** AMWG proposed treatment algorithm for int-2 / high risk MF based on IPSS/DIPSS/DIPSS-plus; **C** AMWG proposed treatment algorithm for overt PMF and SMF based on MIPSS70 + v2.0/GIPSS and MYSEC-PM. AMWG: Asian Myeloid Working Group; PMF: primary myelofibrosis; MF: myelofibrosis; SMF: Secondary MF; int-1: intermediate-1; int-2: intermediate-2; IPSS: International Prognostic Scoring System; DIPSS: Dynamic IPSS; MIPSS70 + v2.0: Mutation-Enhanced International Prognostic Scoring System-plus version 2.0; GIPSS: Genetically Inspired Prognostic Scoring System; MYSEC-PM: Myelofibrosis Secondary to polycythemia and essential thrombocythemia -Prognostic Model; IFN-α: interferon alfa; JAKi: JAK2 inhibitor; WBC: white blood cell; Allo-HSCT: allogeneic hematopoietic stem cell transplantation; MF-SAF: Myelofibrosis-Symptom Assessment Form; QOL: quality-of-life

efficacy of ruxolitinib is expected with concurrent use of CYP3A4 inducers (e.g. rifampicin, phenytoin, barbiturates).

- Patients receiving ruxolitinib are at increased risks of infections, including tuberculosis and hepatitis B virus (HBV) reactivation, both important problems in Asia [240–243]. For patients with a history or prior exposure to tuberculosis, isoniazid prophylaxis may be considered. In HBV carriers and occult HBV carriers (HBV surface antigen negative and anti-HBV core antibody positive), antiviral prophylaxis such as the use of entecavir is recommended due to the high risk of HBV reactivation [207].
- Acyclovir prophylaxis may be considered in patients with a previous history of varicella zoster virus (VZV) reactivation [244].
- The skin should be routinely examined due to the association between ruxolitinib and non-melanoma skin cancer.
- IFNα has limited efficacy in advanced disease and may result in worsening cytopenia or symptoms in patients with intermediate-2/high-risk disease.
- The role of splenectomy is controversial and should only be considered in patients with symptomatic splenomegaly refractory to drug therapy [245]. Alternative, low-dose splenic irradiation may be considered when splenectomy is not feasible.

Role of allo-HSCT in MF

Age, performance status, disease risk and donor availability are the main determining factors of allo-HSCT [86, 246, 247]. It should generally be reserved for patients with IPSS, DIPSS and DIPSS-plus intermediate-2 and high risks [34, 86, 87, 113]. The MIPSS70 + v2.0, and MYSEC-PM may allow better disease risk stratification [113]. Additionally, the myelofibrosis transplant scoring system (MTSS) predicts post-transplantation survivals and transplantation-related mortality [248, 249], facilitating patient selection (supplementary table 15).

Pre-HSCT splenectomy is may be considered in patients with symptomatic splenomegaly resistant to JAK inhibitors [34, 86, 87, 247]. The choice of conditioning depends on

age and performance status [113]. Reduced intensity conditioning (RIC) based on fludarabine and busulfan are most commonly employed [250–252].

AMWG consensus on the role of allo-HSCT for MF

- IPSS, DIPSS or DIPSS-plus should be used to identify transplant-eligible patients who may benefit from allo-HSCT. If NGS data are available, MIPSS70 + v2.0, MYSEC-PM and the MTSS should be used for patient selection.
- HLA-identical sibling donors and matched unrelated donors (MUD) are the two common sources of HSC in Asia.
- Haploidentical allo-HSCT is increasing performed and has achieved similar outcomes.
- Peripheral blood HSCs are generally preferred, which result in earlier engraftment [253].
- RIC is recommended for patients ≥ 55 years old or with comorbidities.
- Management of patients relapsing from allo-HSCT should be individualized. Donor lymphocyte infusion may achieve satisfactory responses. JAK inhibitors should be considered in patients with persistent symptomatic splenomegaly. Second allo-HSCT should be reserved for highly selected individuals.

Management of accelerated / blast phase MF

In transplant-eligible patients, allo-HSCT should be considered [181]. In blast phase MF, disease control should be considered prior to allo-HSCT. Phase 2 studies have demonstrated safety and efficacy of ruxolitinib in combination with hypomethylating agents [254, 255]. Options include intensive chemotherapy or hypomethylating agents such as azacitidine and decitabine as single agent or in combination with ruxolitinib or venetoclax [87, 181]. For patients who are ineligible for allo-HSCT, JAK2 inhibitors and low-intensity therapy is recommended.

AMWG consensus on the management of accelerated / blast phase MF

- Ruxolitinib is recommended for symptom and spleen size control in addition to the use of hypomethylating agents.
- Venetoclax in combination with hypomethylating agents may be considered.
- Intensive chemotherapy is not recommended due to suboptimal response rates and high risks of complications.
- For transplant-ineligible patients, enrollment into clinical trials is encouraged.

Venous thromboembolism in MPN

The American College of Chest Physicians (ACCP) guideline on the management of venous thromboembolism (VTE) and anticoagulation is generally adopted [113, 256]. In addition, cytoreduction with HU for hematocrit and platelet control is essential [181, 184]. Platelet cytapheresis is only rarely required in patients with acute life-threatening thrombotic events and extreme thrombocytosis not responding to cytoreductive therapy [113, 181]. Long-term anticoagulation is generally recommended for recurrent VTE [87, 257].

AMWG consensus on the management of VTE in MPN

- VTE should be managed according to the ACCP guidelines.
- Low molecular weight heparin (LMWH), warfarin or directly-acting oral anticoagulants are therapeutic options depending on age, body weight, comorbidities (such as renal impairment), possible drug-drug interactions and personal preference.
- For the first episode of VTE, the duration of anticoagulation depends on severity, site of thrombosis and likelihood of recurrence. Anticoagulation for a finite duration of 6 months is generally recommended along with cytoreduction.
- Concurrent use of anticoagulation and aspirin is not recommended. After completing the course of anticoagulation therapy, aspirin is resumed [257].
- In patients at high risk of recurrence, such as those experiencing resistance to cytoreduction, a prolonged course of anticoagulation can be considered until the desired result is achieved.

MPN during pregnancy

ET followed by PV are the common MPNs occurring in young women. A small peak in the incidence of ET is observed in women in their thirties [87, 258]. Live birth-rate might be as low as 50–70% if thrombocytosis is not appropriately managed [184, 259, 260]. Adverse pregnancy outcomes include placental abruption, intrauterine growth restriction, and miscarriages [184, 259–261]. Low-dose aspirin is recommended in all patients throughout pregnancy [87, 181, 184]. In patients at high risk of adverse pregnancy outcomes such as prior VTE or miscarriage, the use of LMWH and cytoreduction with IFNα are recommended [113, 181, 184, 260, 261]. LWMH should be continued until 6 weeks post-partum before switching back to aspirin.

AMWG consensus on the management of MPN during pregnancy

- Risk stratification and close monitoring of maternal and fetal well-being is essential prior to delivery.
- In low-risk patients, the presence of fetal distress necessitates the need for LMWH and cytoreduction with IFNα. Peg-IFNα-2a is generally the drug of choice due to its safety and tolerability [87, 113, 259, 261].

Conclusion

In Asia, risk stratification and an individualized approach is recommended for the management of MPN. Every effort should be made to consider the quality of life and the need for disease modification in the treatment algorithm. This consensus also identifies management gaps in Asian patients with MPN, particularly the of availability of advanced molecular techniques in the diagnosis and prognostication of MPN. In addition, there is significant limitation in the choice of available therapies in MPN, due to prolonged delays between drug approvals to availability and re-imbursement in Asia. Based on these limitations, a pragmatic approach in evaluating and treating MPN is necessary. Enrolment to clinical trials should also be considered wherever possible.

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Declarations

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