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REVIEW ARTICLE

Chronic myeloproliferative neoplasms

Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet

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Abstract

This document updates the recommendations on the management of Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-neg MPNs) published in 2011 by the European LeukemiaNet (ELN) consortium. Recommendations were produced by multiple-step formalized procedures of group discussion. A critical appraisal of evidence by using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology was performed in the areas where at least one randomized clinical trial was published. Seven randomized controlled trials provided the evidence base; earlier phase trials also informed recommendation development. Key differences from the 2011 diagnostic recommendations included: lower threshold values for hemoglobin and hematocrit and bone marrow examination for diagnosis of polycythemia vera (PV), according to the revised WHO criteria; the search for complementary clonal markers, such as *ASXL1*, *EZH2*, *IDH1/IDH2*, and *SRSF2* for the diagnosis of myelofibrosis (MF) in patients who test negative for *JAK2*V617, *CALR* or *MPL* driver mutations. Regarding key differences of therapy recommendations, both recombinant interferon alpha and the JAK1/JAK2 inhibitor ruxolitinib are recommended as second-line therapies for PV patients who are intolerant or have inadequate response to hydroxyurea. Ruxolitinib is recommended as first-line approach for MF-associated splenomegaly in patients with intermediate-2 or high-risk disease; in case of intermediate-1 disease, ruxolitinib is recommended in highly symptomatic splenomegaly. Allogeneic stem cell transplantation is recommended for transplant-eligible MF patients with high or intermediate-2 risk score. Allogeneic stem cell transplantation is also recommended for transplant-eligible MF patients with intermediate-1 risk score who present with either refractory, transfusion-dependent anemia, blasts in peripheral blood > 2%, adverse cytogenetics, or high-risk mutations. In these situations, the transplant procedure should be performed in a controlled setting.

Introduction

Over the last few years, significant progress has been made in a number of areas of Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-neg MPNs), i.e., polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). The observation that specific mutations of the calreticulin (*CALR*) gene are present in a significant proportion of patients with ET and MF has further expanded the knowledge of driver mutation profile providing new diagnostic and prognostic opportunities [1, 2]. Additional, non-driver, myeloid gene mutations with prognostic relevance in MF have been identified [3, 4]. Moreover, a

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considerable number of randomized controlled trials have examined pharmacological and non-pharmacological interventions [5–14].

The new strides in the knowledge of Ph-neg MPNs have been matched by unprecedent efforts toward providing physicians with guidance principles and practice recommendations to appropriately translate these novelties into clinical use [15–23]. However, the majority of the published recommendations are based on subjective judgments without rigorous appraisal of existing evidence. Therefore, the decisions on the best management of patients with Ph-neg MPNs remains a challenge requiring a high degree of professional expertize.

This project aims to update the 2011 European LeukemiaNet (ELN) recommendations on the management of Ph-neg MPNs [24]. The goal was to produce consensus-based recommendations in the areas where no scientific evidence is available, and evidence-based recommendations when controlled clinical trials were available.

Methods

An Expert Panel (hereafter referred to as the Panel) of 23 experts was selected for their expertize in research and clinical practice of Ph-neg MPNs. A clinician with expertize in clinical epidemiology (G. Ba.) coordinated the process. During an initial meeting, the subset of key-questions deserving revision among those exploited in the previous guidelines document was chosen. A structured literature search for English-language publications using electronic data-bases such as MEDLINE, 2011–2017 (March) and EMBASE, 2011–2017 (March) was subsequently performed. Publications which measured efficacy of drugs or procedures in individuals with Ph-neg MPNs with a comparison group were critically appraised to rate confidence in estimates of effect for each outcome. For this last objective, we used the methodology of Grades of Recommendation, Assessment, Development and Evaluation (GRADE) [25]. For each trial, we first analyzed the internal validity with use of the Cochrane Collaboration's risk of bias assessment tool [26]. We then evaluated the external validity by assessing four dimensions of trials quality: precision, consistency, directness, and publication bias.

Multiple-step procedures were utilized for achieving recommendations. Two panelists (TB and AT) drafted the updated statements addressing the identified key questions. Subsequently, each panelist scored his/her agreement with those statements and provided suggestions for rephrasing. In order to exploit this phase of the process, a five-round Delphi process was conducted [27].

Results

Diagnostic procedures for Ph-neg MPNs

In patients with clinical or hematologic phenotype of PV, the 2016 revised World Health Organization (WHO) classification uses lower threshold values for hemoglobin and hematocrit [28] (Table 1). These lower thresholds require bone marrow (BM) examination for correct diagnosis [29].

In ET, *CALR* mutations were added to the *JAK2* and *MPL* driver mutations as a major diagnostic criteria [30]. In MF, the 2016-WHO classification distinguishes pre-fibrotic (pre-PMF) from ET and from overtly fibrotic primary MF (PMF) [31]. The diagnosis of post-PV or post-ET MF should be consistent with the criteria published by the International Working Group for MPN Research and Treatment (IWG-MRT) [32].

In addition to the three driver mutations (*JAK2, CALR*, and *MPL*), PV, ET, and MF are all characterized by the optional presence of additional somatic mutations that include *LNK*, *CBL*, *TET2*, *ASXL1*, *IDH*, *IKZF1*, *EZH2, DNMT3A, TP53, NFE2, SF3B1, SRSF2*, *U2AF1* as well as atypical *MPL* or *JAK2* mutations [4, 33, 34]. In the absence of any of the three driver clonal mutations, the search for the most frequent additional mutations is of help in determining the clonal nature of the disease.

Recommendations

In all three categories of Ph-neg MPNs, i.e., PV, ET, and MF, strict adherence to the 2016 revised WHO diagnostic criteria is recommended.

BM biopsy is a necessary diagnostic test in any patient suspected of a Ph-neg MPN, with the exception of patients with PV with a hemoglobin greater than 18.5 g/dL in males and greater than 16.5 g/dl in females.

Peripheral blood or BM screening for driver mutations, i.e., JAK2V617F, CALR, and MPL, is recommended in any patient who may have a Ph-neg MPN.

JAK2V617F should be the first test in patients suspected of any of the three diseases; in the case of JAK2V617F negativity, CALR and MPL, in that order, should then be tested in ET and MF, while JAK2 exon 12 should be tested in those JAK2V617F negative patients suspected of PV.

Search for complementary clonal markers, such as ASXL1, EZH2, IDH1/IDH2, and SRSF2 is recommended in patients who tested negative for the three driver mutations and have BM features and a clinical phenotype consistent with MF.

There was no consensus concerning the search of additional clonal markers such as TP53, TET2, DNMT3A, and CBL in MF, and no consensus concerning the need for

Table 1 World Health Organization (WHO) 2016 diagnostic criteria in chronic myeloproliferative neoplasms

	Polycythemia vera (PV)[a]	Essential thrombocythemia (ET)[b]	Primary myelofibrosis (PMF)[c]	
Major criteria				
			Pre-PMF	Overt PMF[i]
1	Hemoglobin > 16.5 g/dl (men) > 16 g/dl (women) or hematocrit > 49% (men) > 48% (women) or increased red cell mass (RCM)	Platelet count ≥ 450×10^9/l	Megakaryocytic proliferation and atypia,[d] without reticulin fibrosis > grade 1,[e] accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis	Megakaryocyte proliferation and atypia[d] accompanied by either reticulin and/or collagen fibrosis (grade 2 or 3)
2	BM with age-adjusted hypercellularity and trilineage myeloproliferation with pleomorphic, mature megakaryocytes (differences in size)	BM with megakaryocyte proliferation with large and mature morphology. No significant left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers	Not meeting WHO criteria for BCR-ABL1 + CML, PV, ET, MDS, or other myeloid neoplasm	Not meeting WHO criteria for BCR-ABL1 + CML, PV, ET, MDS, or other myeloid neoplasm
3	Presence of JAK2 mutation	Not meeting WHO criteria for BCR-ABL1 + CML, PV, PMF, MDS, or other myeloid neoplasm	Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker[f] or absence of minor reactive bone marrow reticulin fibrosis[g]	Presence of JAK2, CALR, or MPL mutation or in the absence, the presence of another clonal marker[f] or absence of evidence for reactive bone marrow fibrosis[h]
4		Presence of JAK2, CALR, or MPL mutation		
Minor criteria				
1	Subnormal serum erythropoietin level	Presence of a clonal marker (e.g., abnormal karyotype) or absence of evidence for reactive thrombocytosis	Presence of one or more of the following[i]: Anemia not attributed to a comorbid condition Palpable splenomegaly Leukocytosis ≥ 11×10^9/l Elevated LDH[j]	Presence of one or more of the following[i]: Anemia not attributed to a comorbid condition Palpable splenomegaly Leukocytosis ≥ 11×10^9/L Elevated LDH[j] Leukoerythroblastosis

BM bone marrow, *CML* chronic myeloid leukemia, *MDS* myelodysplastic syndrome

[a] PV diagnosis requires meeting either all three major criteria or the first two major criteria and one minor criterion

[b] ET diagnosis requires meeting all four major criteria or first three major criteria and one minor criterion

[c] prePMF diagnosis requires all three major criteria and at least one minor criterion. Overt PMF diagnosis requires meeting all three major criteria and at least one minor criterion

[d] Small-to-large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering

[e] In cases with grade 1 reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (that is, prePMF)

[f] In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (ASXL1, EZH2, TET2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.

[g] Minor (grade1) reticulin fibrosis secondary to infection, autoimmune disorder or another chronic inflammatory condition.

[h] Bone marrow fibrosis secondary to infection, autoimmune disorder or another chronic inflammatory condition

[i] Confirmed in two consecutive determinations.

[j] Above the upper limit of the institutional reference range.

searching for complementary clonal markers in ET. Thus, this decision should follow individual institutional preference.

Risk stratification

Risk stratification in PV and ET

The conventional prognostic systems in PV and ET are based upon age and history of thrombosis, which separate patients into low-risk (age < 60 years and no history of thrombosis) or high-risk (age ≥ 60 years or prior thrombosis) categories [35–37].

In PV, evidence is accumulating that the leukocyte count is implicated in the process of thrombogenesis [38, 39]. However, an intermediate-risk category in PV that includes younger patients with coexisting cardiovascular risk factors or leukocytosis in the absence of previous thrombosis, has not yet been formally validated.

In ET, a new scoring system that includes *JAK2*V617F mutation and general cardiovascular risk factors as predictors of thrombosis (IPSET-thrombosis), has been developed, revised, and validated [40–43] (Table 2).

Recommendations

In PV, age and previous thrombosis history are the prognostic parameters used to classify patients in low-risk and high-risk categories.

In ET, the IPSET-thrombosis system that includes age, previous thrombosis, cardiovascular risk factors, and JAK2V617F mutation, is the recommended prognostic system and it should be scored in all patients at diagnosis.

This implies that general risk factors for thrombosis, including smoking habit, diabetes mellitus, arterial hypertension, and hypercholesterolemia, should also be considered.

Risk stratification in MF

Robust prognostic modeling in primary myelofibrosis (PMF) started with the development of the International Prognostic Scoring System (IPSS) in 2009 [44]. The IWG-MRT subsequently developed a dynamic prognostic model (DIPSS) that can be applied at any time during the disease course [45]. IPSS- and DIPSS-independent risk factors for overall survival (OS) in PMF were subsequently identified: they included unfavorable karyotype [46, 47], the need for red cell transfusion [48, 49], and a platelet count < 100×10^9/l [50]. Accordingly, DIPSS was modified into DIPSS-plus [51] (Table 3).

Recently, the prognostic relevance of driver and additional non-driver mutations was carefully investigated [3, 52]. Authors reported the longest OS in *CALR*$^+$*ASXL1*$^-$

Table 2 The IPSET criteria for evaluating the thrombotic risk of essential thrombocythemia (ET)

Risk factor	HR	Score
Age > 60 years	1.50	1
Cardiovascular risk factors	1.56	1
Previous thrombosis	1.93	2
JAK2V617F	2.04	2

Low risk implies a score = 0–1; intermediate risk, score = 2; and high risk, score ≥ 3

Table 3 Risk stratification of primary myelofibrosis (PMF)

Prognostic model	Risk groups
IPSS	
Risk factors (weight)	Low risk: 0 point
Age > 65 years (1 point)	Intermediate-1 risk: 1 point
Constitutional symptoms (1 point)	Intermediate-2 risk: 2 points
Hemoglobin < 10 g/dl (1 point)	High risk: ≥ 3 points
WBC count > 25×10^9/l (1 point)	
Circulating blasts ≥ 1% (1 point)	
DIPSS	
Risk factors (weight)	Low risk: 0 point
Age > 65 years (1 point)	Intermediate-1 risk: 1–2 point
Constitutional symptoms (1 point)	Intermediate-2 risk: 3–4 points
Hemoglobin < 10 g/dl (2 points)	High risk: 5–6 points
WBC count > 25×10^9/l (1 point)	
Circulating blasts ≥ 1% (1 point)	
DIPSS-plus	
Risk factors (weight)	Low risk: 0 point
DIPSS score low (0 point)	Intermediate-1 risk: 1
DIPSS-int 1 (1 point)	Intermediate-2 risk: 2–3 points
DIPSS-int 2 (2 points)	High risk: 4–6 points
DIPSS high (3 points)	
RBC transfusion need (1 point)	
PLT count < 100×10^9/l (1 point)	
Unfavorable karyotype[a] (1 point)	

RBC red blood cell

[a] (+ 8, -7/7q, i(17)q, -5/5q, 12p-, inv(3), 11q23 rearrangements)

patients (median, 10.4 years) and shortest in *CALR*$^{-}$*ASXL1*$^{+}$ patients (median, 2.3 years). *CALR*$^{+}$*ASXL1*$^{+}$ and *CALR*$^{-}$ *ASXL1*$^{-}$ patients had similar survival and were grouped together in an intermediate-risk category (median survival, 5.8 years) [53, 54]. Furthermore, targeted studies with next generation sequencing have identified *ASXL1*, *SRSF2*, *CBL*, *KIT*, *RUNX1*, and *SH2B3* mutations as having an adverse effect on OS or leukemia-free survival (LFS), but these analyses did not include a multivariate assessment of all factors [55, 56].

It has been claimed that genetic information has the potential to integrate and improve the current prognostic systems [57]. However, the Panel cast doubts on its general clinical utility when used for making therapeutic decisions in MF, except in the setting of allogeneic stem cell transplantation (allo-HSCT) [58].

Recommendations

In MF, the IPSS, based on hematological and clinical variables, is the recommended prognostic system and should be scored in all patients at diagnosis.

There is increasing evidence that integration of IPSS with additional genetic information, i.e., cytogenetics and molecular parameters, allows a more detailed individualized prognostic classification.

For this reason, cytogenetic studies, classification of CALR mutations into type 1/like and type 2/like, and screening for non-driver additional mutations including at least ASXL1 and SRSF2, has become current practice in research centers.

The Panel agreed that a complete genetic assessment should be encouraged in all patients for the prognostic assessment at diagnosis. However, the Panel also claimed that failure to perform a full genetic characterization at the time of diagnosis is acceptable in clinical practice.

DIPSS, based on hematological and clinical variables, or DIPSS-plus, based on hematological, clinical and cytogenetic variables, are the recommended systems for prognostic re-assessment during the disease course.

Molecular assessment during the course of the disease (at least ASXL1 mutation) is recommended for therapeutic decisions in selected MF patients, such as to decide a transplant in those who have an intermediate-1 risk category according to the DIPSS/DIPSS-plus score.

Management of PV

First-line therapy

The ELN-2011 recommendations for first-line therapy of patients with PV include phlebotomy and low-dose acetyl salicylic acid. In high-risk patients either hydroxyurea or recombinant interferon alpha (rIFNα) are the recommended first-line cytoreductive therapies at any age [24].

Recently, in the randomized phase 3 CYTO-PV trial, 365 PV patients were randomly assigned to receive either more intensive phlebotomy treatment (target hematocrit, $<45\%$) or less intensive phlebotomy treatment (target hematocrit, 45 to 50%) [10]. After a median follow-up of 31 months, the primary endpoint, i.e., time until death from cardiovascular cause or major thrombotic events, was recorded in 2.7% patients in the low-hematocrit group and in 9.8% patients in the high-hematocrit group (HR in the high-hematocrit group, 3.91; 95% confidence interval (CI) = 1.45 to 10.53). According to GRADE methodology, we used CI as the primary tool for judging the precision of the results [59]. The low CI boundary of the HR closest to no effect (HR = 1) provided only 0.45-fold greater rate of cardiovascular events in patients with higher-hematocrit target. Thus, the quality of evidence on the precision of benefit was deemed to be low, and the core quality of evidence of the trial was deemed moderate. This indicates that additional research is likely to have important impact on our confidence in the estimate of effect. Notwithstanding, the Panel reasoned that, in a risk-benefit ratio perspective, this result reinforces the previous empirically determined recommendation to maintain the hematocrit lower than 45% [24].

In the dearth of experimental evidence on the effects of iron supplementation in PV patients under TP, the Panel reasoned by focusing on the balance between the discomfort of iron deficiency and the risk of increased hematocrit with iron supplementation.

Phase 2 trials have reported that pegylated interferon alpha-2a can induce durable hematological and molecular responses in patients with PV [60–62].

Recommendations

The Panel strongly recommended that all patients with PV should be managed with phlebotomy to maintain the hematocrit below 45%, together with daily low-dose acetyl salicylic acid.

In the induction phase, phlebotomy regimen should vary from 300 to 450 ml of blood withdrawn weekly or twice weekly until the hematocrit target is reached. Maintenance phase should have the same amount of blood volume removed per phlebotomy as in the induction phase, while the phlebotomy intervals should be determined by the levels of hematocrit.

Cytoreduction is strongly recommended in high-risk cases, i.e., patients with an age older than 60 years, or those with a previous thrombotic event.

The Panel convened that poor tolerance to phlebotomy is an additional indication to cytoreductive therapy.

In the case of documented severe tissue iron deficiency associated with detrimental symptoms (pica, mouth paresthesia, esophagitis, rest-less legs), iron supplementation is indicated. Occurrence of undesired hematocrit worsening due to iron therapy, indicates the need of cytoreduction.

Symptomatic or progressive splenomegaly, severe disease-related symptoms, platelet counts greater than 1500×10^9/l or leukocyte count higher than 15×10^9/l, are further indications to start cytoreductive therapy.

Either hydroxyurea or rIFNα is the first-line cytoreductive therapy at any age. However, the Panel agreed it is wise to adopt a cautionary principle and carefully consider the use of hydroxyurea in young patients.

All patients should be managed aggressively for their cardiovascular risk factors.

Therapy change and second-line therapy

Conventional second-line therapy in PV includes hydroxyurea as a substitute for rIFNα and rIFNα as a substitute of hydroxyurea[24]. Recently, one phase 2 and two phase 3 randomized trials (RESPONSE trials) have reported efficacy of the JAK1/JAK2 inhibitor ruxolitinib in individuals with PV who were resistant or intolerant to hydroxyurea [7, 8, 63]. Following these results, ruxolitinib received approval in 2014 from the US Food and Drug Administration (FDA) and in 2015 from the European Medicine Agency (EMA) for the treatment of patients with PV who have an inadequate response to or cannot tolerate hydroxyurea.

We downgraded the overall quality of evidence for the critical outcomes of RESPONSE trials because we found risk of performance bias, and indirectness in the comparator. On the contrary, we rated the hematocrit response and primary response as having a high level of evidence. Overall, the judgment of the quality of evidence was deemed to be moderate (Appendix 1 for critical appraisal of evidence of the RESPONSE trials).

In a randomized, double-blind, double-dummy, phase 3b trial (RELIEF), PV patients who were well-controlled with a stable dose of hydroxyurea but who reported PV-related symptoms, were randomized to ruxolitinib or hydroxyurea to measure the frequency of patients reaching ≥ 50% improvement from baseline in total symptom score [11]. Ruxolitinib was associated with a non-significant trend towards improved PV-related symptoms vs. hydroxyurea.

Recommendations

PV patients classified as low-risk at diagnosis require the introduction of cytoreductive therapy once they reach the age of 60, or once they develop major thrombotic complications.

The Panel agreed that both rINFα and ruxolitinib are appropriate second-line drug therapies for PV patients who are intolerant or have inadequate response to hydroxyurea. In this setting, the recommendation of use of ruxolitinib was judged by the Panel as strong, even though the confidence in the outcome measures was moderate. In the absence of a direct comparison of the two agents, the choice should be based on the patient's age and drug availability. rINFα should be preferred in young patients in need of long-term treatment.

Intermittent doses of busulphan may be considered in very elderly patients.

Management of ET

First-line therapy

Current guidelines favor hydroxyurea as first-line therapy of ET patients in need of cytoreduction [21]. The recommendation is based on the superiority of hydroxyurea combined with acetyl salicylic acid vs. anagrelide combined with acetyl salicylic acid in the UK-PT1 trial in a cohort of high-risk patients diagnosed on the basis of Polycythemia Vera Study Group criteria [63, 64]. More recent phase 2 trials have reported that pegylated interferon alpha-2a can induce durable hematological and molecular responses in patients with ET [61, 65]. Moreover, in patients with ET strictly diagnosed according to the WHO system and thus excluding early-PMF cases, a phase 3 non-inferiority trial (ANAHYDRET) documented that anagrelide proved non-inferior when compared to hydroxyurea in the prevention of thrombotic complications [9]. The critical appraisal of the trial recognized non-blinded therapy assignment, and indirectness of the population, since patients enrolled in the trial were defined at high-risk according to non-standard criteria (platelet count ≥ 1000×10^9/l and increase of platelet count ≥ 300×10^9/l within 3 months). However, the precision of the results was considered high. Finally, the evidence that anagrelide is comparable with hydroxyurea was judged moderate.

The 2011-ELN guidelines indicate that all patients with ET should be managed with low-dose acetyl salicylic acid if microvascular disturbances are present [24]. New observations have delineated the appropriate use of acetyl salicylic acid as a prevention of vascular events in ET patients. In a retrospective study, the rate of major thrombosis was significantly lower in the subgroup of patients ≥ 60 years when used in association with cytoreductive therapy, and compensates the increased risk of bleeding [66]. In a retrospective analysis, antiplatelet therapy in CALR-mutated patients did not affect the risk of thrombosis but was associated with higher incidence of bleeding, while in *JAK2*V617F-mutated patients, low-dose acetyl salicylic

acid was associated with a reduced incidence of venous thrombosis with no effect on the risk of bleeding [67]. Recently, Barbui and co-workers [68] delineated a category of "very-low risk" ET, i.e., patients without cardiovascular risk factors, age ≤ 60 years and *JAK2*-unmutated.

Recommendations

In high-risk ET, three drugs have provided evidence of being able to produce hematological response, i.e., hydroxyurea, rINFα, and anagrelide.

The Panel agreed on recommending hydroxyurea and rINFα as first-line therapy agents.

Even though the majority of the experts indicated anagrelide as an appropriate choice for first-line therapy in ET, the Panel did not reach a consensus on recommending the agent in this setting, arguing that the evidence of non-inferiority with hydroxyurea was of insufficient quality, and the risk-benefit ratio unfavorable.

The use of cytoreductive drugs in otherwise low- or intermediate-risk patients carrying well-controlled cardiovascular risk factors is not generally recommended.

From the results of retrospective observational studies, all patients with IPSET-thrombosis high-risk disease should receive low-dose acetyl salicylic acid. Patients with low- or intermediate-risk ET should receive low-dose acetyl salicylic acid when age is ≥ 60 years, or when uncontrolled cardiovascular risk factors or JAK2V617F mutation are present.

Therapy change and second-line therapy

The 2011-ELN guidelines claimed that in case of refractoriness or intolerance to first-line therapy with hydroxyurea [69], non leukemogenic drugs such as anagrelide or rINFα should be recommended [24].

Recommendations

Patients with ET should start a cytoreductive treatment as soon as they shift to the high-risk category by reaching the age of 60 years or by the occurrence of a major thrombotic or hemorrhagic event. Increasing platelet count above 1500×10^9/l is an additional indication to cytoreductive therapy.

Cytoreduction may be also required for progressive myeloproliferation (e.g., increasing splenomegaly) or uncontrolled ET-related systemic symptoms.

Anagrelide or rINFα are the recommended second-line therapy of ET after hydroxyurea.

Management of MF

Since the recommendations on the management of MF published in 2011 [24], a number of new therapeutic agents have been proposed and some of them have been experimentally tested [5, 6, 12–14, 70–74]. Among these, ruxolitinib has been approved both by FDA and EMA. The Panel was thus questioned whether the new targeted therapy proved to favorably modify the natural history of the disease, or significantly prolong survival. By applying GRADE methodology, we derived pooled estimates across the two randomized controlled trials (COMFORT trials) and we calculated pooled HRs and 95% CIs using random-effect models for all-cause mortality [75]. We documented a significant benefit associated with ruxolitinib treatment at late follow-up. Our meta-analysis, however, failed to meet the "optimal information size" criteria: thus, we downgraded the confidence in the estimates of survival advantage of ruxolitinib for imprecision (too few events) [59]. A similar analysis was published by the Cochrane collaboration [76], and later on by Cervantes and co-workers [77]. These results suggested that the evidence from the two COMFORT trials on improved survival in MF patients treated with ruxolitinib is moderate to poor. Therefore, the Panel agreed that moving to a disease-oriented therapeutic strategy with ruxolitinib for MF was not justified, and the revised recommendations were issued across the different phenotypes/problems of the disease.

Asymptomatic patients with low- or intermediate-1 risk disease

There is no evidence to support the value of disease-modifying therapy in patients with IPSS/DIPSS/DIPSS-plus low or intermediate-1 risk disease. However, some of these patients might require palliative therapy for anemia, splenomegaly, or constitutional symptoms, as recommended in the previous guidelines [24].

Recommendations

We recommend observation alone for IPSS/DIPSS/DIPSS-plus low- or intermediate-1 MF risk patients who lack significant symptoms, and who do not display significant anemia (hemoglobin < 10 g/dl), splenomegaly (palpable spleen size > 10 cm), leukocytosis (leukocyte count > 25×10^9/l), or marked thrombocytosis (platelet count > 1000×10^9/l).

If cytoreductive treatment for the reduction of leukocytosis or thrombocytosis is indicated, the first-line drug of choice is hydroxyurea.

Treatment of MF-associated anemia

According to the 2011-ELN recommendations, treatment of MF-associated anemia includes androgens, prednisone, epoetins, danazol, thalidomide, or lenalidomide [24].

Recently, pomalidomide, a thalidomide analog, has been tested in a number of phase 2 and one phase 3 trial [12,78–84]. In a phase 3 randomized trial, 252 transfusion-dependent subjects were randomly assigned (2:1) to pomalidomide or placebo [12]. Trialists and subjects were blinded to treatment allocation. Pomalidomide and placebo achieved similar RBC-transfusion-independence response rates (16%).

At the end, no evidence-based recommendations for the best strategy of treating MF-associated anemia can be issued. The Panel discussed the limitations of conventional drug therapy on the basis of case reports [85, 86], and clinical experience.

Recommendations

The choice of a specific drug for MF-associated anemia should be based on overall toxicity profile and its expected risk in the individual patient.

Androgen preparations should be avoided in patients with prostate disease or concomitant liver disease.

Thalidomide and its analogs should be avoided in patients with documented peripheral neuropathy grade 2, and its use should be strictly monitored in those with grade 1 neuropathy or who are at risk for such complication such as diabetics.

In patients with transfusion dependency, a low rate of response to epoetins is expected, therefore the risk/benefit of a therapeutic use with epoetins is questionable.

Lenalidomide use is justified in cases with the presence of del(5q31).

There is currently not enough evidence to recommend combination therapy for MF-associated anemia, other than the addition of a short course of prednisone therapy to treatment with thalidomide.

Treatment of MF-associated splenomegaly

Conventionally, first-line therapy for MF-associated splenomegaly is hydroxyurea [24]. Since the major benefits of ruxolitinib therapy in MF were the reduction in splenomegaly and amelioration of MF-related symptoms [6, 87, 88], these results challenged the primary use of hydroxyurea in this indication. A GRADE analysis of COMFORT trials documented that the overall quality of evidence supporting the benefit of ruxolitinib in reducing splenomegaly in patients with intermediate-2 or high-risk disease was high, due to the randomized design, a clear demonstration of a dose–response relationship between ruxolitinib dose and spleen volume reduction. However, the quality of evidence was reduced due to unblindness and serious indirectness of the comparator [75]. For these limitations, the Panel argued for a limited use of the drug in the therapy of splenomegaly in MF. For low-intermediate-1 patients, the Panel reasoned that the extent of the benefit identifying the threshold for treatment is a function of the prognosis of patients and the toxicity/inconveniences of therapy. Thus, patients with low-risk disease were judged to have no indication of use of ruxolitinib, while intermediate-1 disease are candidates to therapy only when symptoms in need of treatment are present.

Recommendations

Ruxolitinib is recommended as first-line approach for MF-associated splenomegaly in patients with intermediate-2 or high-risk disease.

In patients with intermediate-1 risk disease and highly symptomatic splenomegaly, i.e., with the presence of local symptoms, or impairment of food intake, first-line therapy is ruxolitinib.

In other patients with intermediate-1 risk disease, and in those with low-risk disease in need of therapy for MF-associated splenomegaly, hydroxyurea is recommended as first-line therapy.

Ruxolitinib is also recommended for reducing splenomegaly in patients with splenomegaly not responding or intolerant to hydroxyurea.

Allogeneic stem cell transplantation

Current guidelines candidate to allo-SCT those patients with intermediate-2 or high-risk disease [24]. The emergence of new prognostic predictors, such as MF-associated mutations [3, 4, 33, 34], adverse cytogenetics [46, 47], high need of transfusions [48, 49], or high number of circulating blasts [89], drew the Panel to discuss the value of new detrimental markers in widening the transplant indication, particularly in those patients who have an intermediate-1 risk disease. In a recent study on the impact of molecular genetics on the outcome after allo-SCT [90], patients with *ASXL1* mutations had a lower transplant success rate than all comers. The Panel judged this result as preliminary due to the small number of patients analyzed. Moreover, the Panel argued that there is no evidence that allo-SCT cannot overcome the risks associated with the *ASXL1* mutational pattern. Thus, the Panel favored considering allo-SCT in these patients.

Recommendations

We recommend considering allogeneic stem cell transplant for all transplant-eligible patients with IPSS/DIPSS/DIPSS-plus high or intermediate-2 risk.

The Panel also recommended consideration of allogeneic stem cell transplantation for transplant-eligible patients with

IPSS/DIPSS/DIPSS-Plus intermediate-1 risk score who present with either refractory, transfusion-dependent anemia, a percentage of blasts in peripheral blood > 2% in at least two repeated manual measurements, adverse cytogenetics, or high-risk mutations,

In this situation, the transplant procedure should be performed in a controlled setting (registries, clinical trial).

Splenectomy

In patients with symptomatic and progressive splenomegaly, which proved to be resistant to medical therapy, in particular to hydroxyurea, ruxolitinib, or experimental therapies, splenectomy necessarily remains an option [91]. Recent reports on splenectomy in MF [90, 92] have confirmed the seminal results derived from the largest series of cases [93, 94].

Recommendations

Splenectomy remains a viable palliative treatment option for drug-refractory symptomatic splenomegaly and may be considered when drug-induced anemia hampers the effective use of hydroxyurea or ruxolitinib.

Discussion

Consensus techniques and careful revision of new evidences were used to update recommendations for the management of Ph-neg MPNs published in 2011 [24]. The GRADE method, allowed the explicit use of factors that can increase or decrease the quality of the evidence. Although most recommendations remained unchanged, some key differences emerged. Changes included the criteria for the diagnosis, refinement of risk stratification, and the recommendation for therapy of PV and MF due to the emergence of the new anti-JAK1/JAK2 drug, ruxolitinib.

With the rapid development of scientific knowledge, new evidence is emerged between the time we collected the relevant literature for this project and the time we wrote the manuscript. Indeed, a clinical-molecular prognostic model (the MYSEC-PM) to predict OS in patients with post-PV and post-ET MF has been proposed that could improve the prognostic classification of these patients [95]. New predictive factors for anemia response to erythropoiesis-stimulating agents in MF have been analyzed [96]. A randomized controlled phase 3 trial compared a new PEG-proline-IFN-alpha-2b to hydroxyurea (PROUD-PV trial) resulting in a non-inferior efficacy and higher tolerability of PEG-proline-IFN [97, 98]. Finally, a randomized phase 2 trial comparing ruxolitinib to best available therapy in patients with ET resistant or intolerant to hydroxyurea (MAJIC trial) documented that ruxolitinib is not superior to current second-line treatments for ET [99].

As such, these recommendations, though currently accurate, will likely need to be updated in the future.

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Author contributions TB, AT, and GBa developed the study design. GBa did the critical appraisal of evidence of the randomized trials. TB and AT wrote the first draft of the recommendations. All the authors participated to the consensus meetings. GBa wrote the manuscript. All authors critically revised, reviewed, and approved the final version of this study.

Compliance with ethical standards

Conflict of interest TB received advisory board fee from Novartis; FC received advisory board fee from Novartis, honoraria from Novartis, AOP Orphan Disease and Shire, and speaker bureau fee from Novartis, AOP and Shire; AMV received advisory board fee from Novartis, and Speaker bureau fee from Novartis and Shire; MM received speaker bureau fee from Gilead and Amgen; SK received research funding from Novartis, Bristol-Myers Squibb, and Janssen, honoraria and advisory board fees from Novartis, Incyte/Ariad, Pfizer, Bristol-Myers Squibb, Janssen, AOP, CTI, and travel support from Shire; AR received advisory board fee and honoraria from Novartis; MG received honoraria from Shire, Novartis, Baxalta, AOP Orphan Disease, Gilead and Janssen; JJK received advisory board fee and funding from Novartis and AOP Orphan; AB received honoraria form Novartis, Therakos, Sanofi and Adienne, and advisory board fee from Novartis; MFMM received honoraria and consulting fee from Novartis and Gilead; SV received support for research from: Incyte Corporation, Roche, Astra Zeneca, Lilly Oncology, NS Pharma, Bristol Mayers Squibb, Celgene, Gilead, Seattle Genetics, Promedior, CTI BioPharma Corp., Galena BioPharma, Pfizer, Genentech, Blueprint Medicines Corp.; RM received consulting fee from Novartis, AOP, Shire, and research funding from Incyte, Gilead, Pharmessential, Celgene and Promedior; R Ho received research funding from Incyte and Janssen; FP served on advisory boards for Sanofi, Gilead, Janssen Pharmaceutical, Celgene, Novartis, Bristol-Myers Squibb and Roche; GB received advisory board fee from Novartis. GF and G Bi have no conflict of interest.

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