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REVIEW

Essential thrombocythaemia: A contemporary approach with new drugs on the horizon

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Summary

Essential thrombocythaemia (ET) is a myeloproliferative neoplasm characterized by an increased risk of vascular complications and a tendency to progress to myelofibrosis and acute leukaemia. ET patients have traditionally been stratified into two thrombosis risk categories based on age older than 60 years and a history of thrombosis. More recently, the revised IPSET-thrombosis scoring system, which accounts for the increased risk linked to the *JAK2* mutation, has been incorporated into most expert recommendations. However, there is increasing evidence that the term ET encompasses different genomic entities, each with a distinct clinical course and prognosis. Moreover, the effectiveness and toxicity of cytoreductive and anti-platelet treatments differ depending on the molecular genotype. While anti-platelets and conventional cytoreductive agents, mainly hydroxycarbamide (hydroxyurea), anagrelide and pegylated interferon, remain the cornerstone of treatment, recent research has shed light on the effectiveness of novel therapies that may help improve outcomes. This comprehensive review focuses on the evolving landscape of treatment strategies in ET, with an emphasis on the role of molecular profiling in guiding therapeutic decisions. Besides evidence-based management according to revised IPSET-thrombosis stratification, we also provide specific observations for those patients with *CALR*-, *MPL*-mutated and triple-negative ET, as well as cases with high-risk mutations.

KEYWORDS
essential thrombocythaemia, myeloproliferative neoplasms, new drugs

INTRODUCTION

Chronic myeloproliferative neoplasms (MPN) are clonal disorders of haematopoietic stem cells characterized by the proliferation of one or more myeloid lineages (granulocytic, erythroid or megakaryocytic) in the bone marrow (BM). Among them, polycythaemia vera (PV), essential thrombocythaemia (ET) and myelofibrosis (MF) have traditionally been encompassed under the term of classic Philadelphia-negative MPN due to their shared clinical features with a common molecular basis.[1–3] Their pathogenesis involves the activation of the JAK–STAT pathway, resulting in hypersensitivity of haematopoietic stem cells to growth factors and cytokines, and leading to overproduction of mature and functional blood cells.[3,4]

From the molecular perspective, the *JAK2*V617F mutation is present in 50%–60% of patients with ET, whereas mutations in the *CALR* and *MPL* genes are detected in 20%–30%

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and 5% of cases respectively. The remaining 10%–15%, the so-called 'triple negatives', may have mutations in other genes associated with myeloid disorders, such as *ASXL1*, *DNMT3A*, *TET2*, *EZH2*, *IDH1/2*, *RUNX1*, *SRSF2*, *SF3B1* and TP53 among others.[3,4]

Among the classical MPN (with an incidence of less than 6 per 100 000 person-years), ET is the most frequent (0.6–2.5 cases per 100 000 population/year).[5] It is also the one with the best prognosis.[6] Despite these neoplasms being typically associated with old age,[5] up to 15% of ET patients are younger than 40 years of age.[6] Survival is mainly determined by vascular complications (thrombotic and haemorrhagic events) and progression to secondary MF or, less frequently, to acute myeloid leukaemia (AML).[7] Progression risk to MF and AML increase with time, with post-ET MF progression rates ranging from 0.8% to 5% at 10 years and up to 15% at 15 years.[8,9] This is particularly relevant in patients diagnosed at a young age, as it directly impacts their life expectancy. A study including 126 patients younger than 40 years at ET diagnosis, with a median follow-up of 10 years, showed a cumulative incidence of MF at 10 years of 3%.[10]

Despite advances in our understanding of the genetic and microenvironmental aspects of this MPN, the management of ET has not changed substantially over the last decade. However, there is increasing evidence that the term ET encompasses different genomic entities, each with a distinct clinical course and prognosis.[11] In the present manuscript, we present our insights on the conventional treatment of ET and the role of new drugs. We outline our view of the current therapeutic approach to this disease in clinical practice.

RISK STRATIFICATION

ET patients have traditionally been stratified into two thrombosis risk categories based on whether they are older than 60 years and have a history of thrombosis. In addition, due to the elevated risk of bleeding associated with extreme thrombocytosis, patients with a platelet count >1500 × 10^9/l are also included in the high-risk category. A subanalysis of the PT-1 trial demonstrated that thrombocytosis during follow-up is correlated with the immediate risk of major haemorrhage in high-risk ET.[12] Other risk factors for bleeding include acquired von Willebrand disease (AVWD) and the use of anti-platelet therapy.[13-16]

More recently, the International Thrombosis Prognostic Score for Essential Thrombocythemia (IPSET-thrombosis) considers the presence of cardiovascular risk factors (diabetes, arterial hypertension and smoking) and the *JAK2*V617F mutation, in addition to classical risk factors.[17] The IPSET-thrombosis stratification defines three risk groups: low, intermediate and high risk, with corresponding thrombosis rates of 1.03%, 2.35% and 3.56% per year respectively.[17]

A subsequent revision of the IPSET has further refined prognostic stratification, establishing four risk groups.[18,19] The main finding of this study was the identification of a very low-risk group exhibiting thrombosis rates comparable to the general population. Furthermore, high-risk categorization was restricted to patients with a history of thrombosis of any age or those older than 60 carrying the *JAK2*V617 mutation (Table 1). However, the proposal of an intermediate-risk group constituted by *JAK2*V617F-negative patients older than 60 years without a history of thrombosis, has been difficult to implement in clinical practice because these patients were classically treated with cytoreduction. Table 1 shows the rates of thrombosis according to the revised IPSET-thrombosis stratification.[18,19]

A recent study from the Spanish MPN group (GEMFIN) evaluated IPSET-thrombosis and revised IPSET-thrombosis scores as predictors of thrombosis in a large cohort of ET patients with prospective follow-up. While both scales proved useful for identifying a high-risk group, they failed

TABLE 1 Incidence rate of thrombosis in essential thrombocythaemia according to the revised IPSET in the original cohort[17] and in a large real-world study.

	Original cohort			Spanish registry		
Risk group	***N***	**Events/person years**	**[a]Rate %patients/year**	***N***	**Events/person years**	**Rate %patients/year**
Very low Age <60 years, JAK2-, no thrombosis	236	10/NP	0.4–1.05	211	11/1525	0.7
Low Age <60 years, JAK2+, no thrombosis	265	29/NP	1.6–2.6	319	16/2188	0.7
Intermediate Age >60 years, JAK2-, no thrombosis	155	14/NP	1.4–1.6	207	10/1286	0.8
High Age >60 years and JAK2+ or history of thrombosis	358	55/NP	2.4–4.2	629	69/3520	1.96

Abbreviation: NP, time at risk not provided.

[a]Rates correspond to the absence and presence of cardiovascular risk factors respectively.

to discriminate among lower risk categories (very low, low and intermediate) and did not predict venous thrombosis (Table 1). Notably, the rate of arterial thrombosis in young patients with *JAK2*V617F-mutated ET or in *JAK2*V617F-negative patients of any age resembled that of the general population, while an increased incidence of venous thrombosis was observed in ET of any age, particularly in the young patients.[20]

A limitation of these prognostic approaches is their primary focus on thrombotic risk, neglecting other clinically relevant aspects, such as the increased risk of bleeding or progression to more advanced stages. Thus, prognostic scales have been developed to incorporate the presence of mutations in high-risk genes (*TP53*, *SF3B1*, *SRSF2* and *U2AF1*), which have been shown to predict overall survival, MF- or leukaemia-free survival (MIPSS-ET).[21] In addition, a multicentre study involving 1607 patients showed that *JAK2*V617F VAF >35%, *CALR* type 1/1-like or *MPL* mutations were predictors of fibrotic progression.[22] Recently, a molecular classification of MPN allowed the identification of eight genomic groups with different outcomes in terms of survival, thrombotic complications and progression.[23] The frequency of these eight molecular groups in ET is outlined in Table 2.

Notably, these classifications have the potential to personalize treatment goals for individual patients but have not yet been incorporated into clinical practice for risk-adjusted therapy.

The primary goal of treatment in ET patients is to prevent vascular complications, minimize the risk of progression to MF or AML and control the symptoms derived from the disease. Currently, available treatments are unable to significantly alter the natural course of the disease, delaying or preventing its progression to more advanced forms.

However, recent studies in PV have challenged this option, as illustrated by the high molecular response rate with ropeginterferon in the PROUD-CONTI trial,[24] and a longer event-free survival in patients achieving complete haematological response and sustained molecular responses in the MAJIC-PV study.[25] Further studies are needed to ascertain whether these findings can be extrapolated to patients with ET.

TABLE 2 Genomic classification of 1326 patients with essential thrombocythaemia according to NGS using the algorithm described by Grinfeld et al.[23]

Genomic subgroup	Percentage	Clinical characteristics
TP53 disruption aneuploidy	2	High risk of AML and early death
Chromatin/ spliceosome aberrations	8	High risk of AML, MF and death
CALR mutation	24	Good outcome
MPL mutation	4	Lower survival
Homozygous *JAK2* mutation	3	PV and MF progression
Heterozygous *JAK2* mutation	44	Majority of patients; Good outcome
Other mutation	2	Good outcome
No mutation	13	Young women; Benign outcome

Note: Patients were hierarchically allocated to eight genomic subgroups. *TP53* mutations, aberrations at chromosome 17p and deletions at chromosome 5q identified the first subgroup, regardless of the driver mutation. The second subgroup was defined by the presence of one or more mutations in *EZH2, IDH1, IDH2, ASXL1, PHF6, CUX1, ZRSR2, SRSF2, U2AF1, KRAS, NRAS, GNAS, CBL* or LOH at chromosome 4q, and aberrations in chromosomes 7 and 7q, regardless of the driver mutation. Patients who were not identified in the above two subgroups were classified according to their dominant phenotypic driver mutation (*CALR*, *MPL* and *JAK2*). A seventh subgroup had identifiable driver mutations such as *TET2* or *DNMT3A* but none of the class-defining drivers identified above.

RISK-ADAPTED THERAPY

Currently, the European LeukemiaNet recommends using the IPSET-thrombosis score to assess thrombosis risk,[26] while the NCCN recommends using the revised IPSET-thrombosis for decision-making regarding thrombosis prevention strategies.[27]

Our general approach to stratify patients and select therapy is based on the revised IPSET-thrombosis score, as shown in Table 3. Careful observation seems to be safe in very low-risk patients (*JAK2*V617-unmutated, age <60 years, no history of thrombosis) since the incidence of thrombosis is similar to that of the general population and primary prophylaxis with low-dose aspirin was associated with an increased risk of bleeding.[13,14] Low-risk patients (*JAK2*V617-mutated, age <60 years, no history of thrombosis) are

TABLE 3 Personal management of essential thrombocythaemia based on risk stratification by the revised IPSET-thrombosis.

	Very low Age ≤60 years, no history of thrombosis, JAK2V617F unmutated	Low Age ≤60 years, no history of thrombosis, JAK2V617F mutated	Intermediate Age >60 years, no history of thrombosis, JAK2V617F unmutated	High Age >60 years and JAK2V617F mutated OR history of thrombosis
Initial therapy	Careful observation*	Low-dose aspirin	Cytoreduction alone	Cytoreduction plus low-dose aspirin
Other clinical factors	Consider cytoreduction if platelet count >1500 × 10^9/l, AVWD, bleeding or persistent microvascular symptoms *Consider low-dose aspirin if CVRF		Consider low-dose aspirin if CVRF	Anticoagulation instead of low-dose aspirin if atrial fibrillation or venous thrombosis

Abbreviations: AVWD, acquired von Willebrand disease defined as ristocetin cofactor activity <30%; CVRF, uncontrolled cardiovascular risk factors.

candidates for primary prevention of thrombosis with low-dose aspirin, which might be useful for reducing venous thrombosis, and arterial thrombosis in those with cardiovascular risk factors.[13,14] The PT1-intermediate trial failed to demonstrate any benefit of adding cytoreduction to anti-platelet therapy in a cohort of patients comprising mainly low-risk patients if the revised IPSET stratification had been applied.[28]

Although the incidence rate of thrombosis in intermediate-risk ET (age >60 years, *JAK2*V617-unmutated, no history of thrombosis) is similar to that in lower-risk categories, using cytoreduction is the most pragmatic approach. It should be taken into consideration that data on careful observation is limited in this category; there is no concern for long-term exposure to cytoreduction in this older subpopulation, and improving haematological control might also be beneficial for reducing symptoms and bleeding risk.[20] We suggest adding low-dose aspirin to intermediate-risk ET only in patients with cardiovascular risk factors, although this approach may be controversial.[29] High-risk patients are candidates for cytoreduction plus low-dose aspirin or anticoagulation when indicated (atrial fibrillation, venous thrombosis etc).

Finally, cytoreduction is also recommended in very low–/low–/intermediate-risk patients with extreme thrombocytosis (platelet count $>1500\times10^9$/l) or AVWD in order to prevent bleeding; in patients with marked myeloproliferation (increasing leucocytosis and/or progressive splenomegaly); major bleeding; or those with disease-related symptoms refractory to anti-platelet therapy.[26,27,30]

ANTI-PLATELET THERAPY

The role of anti-platelet therapy as the primary prophylaxis of thrombosis in low-risk ET patients has not been studied in randomized clinical trials. Recommendations for its use are based on extrapolation from studies in PV (e.g. the ECLAP study)[31] and observational studies in ET.[13,14,29]

A study involving 300 subjects with low-risk ET treated with anti-platelet therapy or careful observation showed an increased risk of venous thrombosis in *JAK2*V617F-positive patients not receiving anti-platelet medication and increased rates of arterial thrombosis in patients with cardiovascular risk factors while on observation, whereas a fivefold increase in the risk of major bleeding was observed in patients with a platelet count greater than 1000×10^9/L receiving anti-platelet therapy.[14]

A subsequent international study including 433 patients with low-risk ET (271 with the *CALR* mutation and 162 with the *JAK2*V617F mutation) showed that in *CALR*-mutated patients, anti-platelet therapy did not affect the risk of thrombosis but was associated with a higher incidence of bleeding.[13] In *JAK2*-mutated patients, anti-platelet therapy reduced the risk of venous thrombosis with no effect on the risk of bleeding. The risk of arterial thrombosis was driven by cardiovascular risk factors (CVRF) and leucocytosis only in *JAK2*-mutated patients, but the protective effect of anti-platelet therapy in this subgroup of patients could not be demonstrated.[13]

A retrospective study including 193 '*classic high-risk*' ET patients (age >60 years without a history of thrombosis) showed that primary prevention with low-dose aspirin plus cytoreduction was superior to cytoreduction alone, with the higher benefit being observed in patients with cardiovascular risk factors or the *JAK2*V617F mutation.[29]

Based on these studies, primary prophylaxis with anti-platelet therapy might be recommended in individuals carrying the *JAK2*V617F mutation (low- and high-risk revised IPSET-Thrombosis), whereas no benefit has been demonstrated for the very low and intermediate revised IPSET categories. Our recommendations for anti-platelet therapy according to the revised IPSET are shown in Table 3.

Secondary prophylaxis with low-dose aspirin has been shown to have substantial net benefit in patients who already had occlusive vascular disease.[32–34] A retrospective study including 494 PV/ET patients with a history of previous thrombosis showed that the addition of anti-platelet therapy improves the protective effect of cytoreduction for secondary prevention of thrombosis. These data support the use of anti-platelet therapy in all ET patients with a history of thrombosis.[35]

Recent studies have shown incomplete platelet inhibition (measured as serum thromboxane B2 level) with once-daily dosing of acetylsalicylic acid (ASA), especially in ET patients not receiving cytoreduction, which could be improved by drug dosing every 12 h.[36] Indeed, some authors recommend a wide use of double aspirin in low-risk ET.[37,38] It remains to be determined, however, whether this schedule would translate into an improvement in the prevention of cardiovascular risk without increasing bleeding. In the absence of randomized data supporting the benefit of anti-platelet therapy as the primary prophylaxis of thrombosis in ET, we do not recommend this approach in low-risk patients not receiving cytoreduction unless symptoms are present. In high-risk patients, especially those with a history of arterial thrombosis, twice-daily dosing might be considered when thrombocytosis is inadequately controlled by cytoreduction.

CYTOREDUCTIVE TREATMENT

Four cytoreductive drugs are available in Europe for the treatment of ET: hydroxycarbamide (HC), pegylated interferon (peg-INF), anagrelide and busulfan. While all of them are effective in achieving haematological responses, only HC and busulfan are approved for first-line use in ET.

Both the ELN and the NCCN guidelines recommend the use of HC in first line.[26,27,39] In young ET patients, peg-INF may be preferred over HC due to its lack of teratogenic or carcinogenic effect. This recommendation is based on phase 2 studies reporting that peg-IFN alpha-2a could induce durable haematological and molecular responses.[26]

A recent meta-analysis comprehensively examined data from 30 studies conducted in MPN with INF until 2019. These studies comprised 12 phase 2 trials, 1 phase 1 trial and 17 cohort studies, 13 of which were prospective, for a total population of 730 patients with ET.[40] Histological response data were reported in only six of the studies, showing histopathological normalization rates ranging from 6% to 30% of patients. Concerning molecular responses in two studies, the ranges of complete (*JAK2* V617F undetectable) and partial MR (≥50% reduction in allele burden) were 9%–27% and 17%–33% respectively.[40,41] After the publication of the ELN guidelines, a phase 3 trial (the MPD-RC 112) compared peg-INF with HC as a first-line treatment in patients with PV and ET.[42] Unfortunately, this trial was prematurely closed due to the unavailability of peg-INF when only 160 patients with MPN were included, of whom 48% had ET, with a median treatment duration of 81 weeks. There was no difference between both arms regarding vascular complications or disease progression, but grade 3 and 4 adverse effects occurred more frequently in the peg-INF arm (46% vs. 28%). At 12 months, there was no difference in complete response rates. However, at 36 months, complete remissions with peg-INF were twice as frequent as those achieved with HC (33% vs. 17%). At 24 months, peg-INF induced a greater reduction in *JAK2*V617F allele burden than HC, although no histological differences were observed among both arms.[42] The Daliah trial reported a higher reduction of *JAK2*V617F allele burden in MPN patients achieving complete haematological response, whereas the CALR variant allele frequency did not significantly decline with IFN.[43] Moreover, a higher frequency of mutations outside the JAK pathway, especially in DNMT3A, in patients failing to achieve molecular response has been reported.[43,44]

With regard to anagrelide, the PT-1 study demonstrated the superiority of HC combined with ASA over anagrelide plus ASA in a cohort of high-risk ET patients.[45] Anagrelide plus ASA showed significantly higher rates of arterial thrombosis, bleeding and transformation to MF, although fewer venous thromboses were observed in this treatment arm. In a phase 3 non-inferiority trial of anagrelide versus HC, which enrolled 255 patients diagnosed with ET according to WHO criteria (excluding prefibrotic MF), comparable thrombotic and bleeding event-free survival (EFS) rates and progression to MF were reported in both arms, after 9 years of follow-up.[46] Due to the higher rate of cardiovascular side effects in patients treated with anagrelide, a phase 4, prospective, non-interventional, postauthorization study (the EXELS study) was conducted, involving more than 3400 patients with ET (WHO criteria or PVSG) in 13 European countries. Patients receiving anagrelide showed a thrombotic event rate similar to that observed with other treatments, but a higher rate of bleeding and transformation to MF.[47] Considering these studies, anagrelide was approved by the EMA as a second-line treatment for patients who were resistant or intolerant to previous therapies.

Practical recommendations for managing these drugs, including initial doses, dose adjustment, contraindications or special precautions, are presented in Table 4.

CRITERIA FOR CHANGING TREATMENT AND CHOICE OF SECOND-LINE DRUG

Patients who meet any of the criteria for resistance or intolerance to HC are candidates for a second-line treatment. These criteria are as follows[48]:

- Platelet count $>600\times10^9$/l despite maximal doses of HC (2 g/day) for 3 months or at the maximum tolerated dose
- Platelets $>400\times10^9$/l and leucocytes $<2.5\times10^9$/l at any dose of HC
- Platelets $>400\times10^9$/l and Hb <10 g/dL at any HC dose
- Fever associated with HC treatment
- Skin ulcers or any other unacceptable mucocutaneous toxicity

TABLE 4 Conventional cytoreductive therapy employed in the treatment of essential thrombocythaemia.

	Hydroxycarbamide	Anagrelide	Peg-interferon
Presentation	500 mg, oral	0.5 mg, oral	90, 135, 180 μg; sc
Initial dose	500–1000 mg/day	0.5 mg/12 h	45–90 μg /week
Maximum dose	2000 mg/day	2.5 mg is the maximum recommended single dose (5 capsules at a time)[a]	180 μg/week
Contraindications and precautions	Skin ulcers Hepatic/renal insufficiency	Hepatic/renal insufficiency (Cr <50 mL/min) Arrhythmias, heart failure	Autoimmune disease Severe psychiatric disorders Severe heart disease Cirrhosis
Recommendations	Sun avoidance	No caffeine or theine consumption	Night-time administration + acetaminophen
Pregnancy	Prohibited	Prohibited	Allowed

[a]Doses up to 10 mg/day have been used during clinical development.

The choice of second-line treatment will depend on the initial therapy used. Anagrelide or peg-INF is recommended as second-line treatment after HC.[26,27] There is no direct comparison between these two drugs to provide information on which one might be more advantageous in this clinical setting, although the controlled SURPASS-ET trial (NCT04285086) comparing ropeginterferon alfa-2b with anagrelide in ET patients resistant or intolerant to HC is ongoing.[49] In the meantime, Peg-INF is preferred for young patients, especially women of childbearing age, and in patients with *CALR*-mutated ET, supported by one study including 31 *CALR*-mutated ET patients mostly receiving second-line Peg-IFN and reporting rates of complete haematological response, complete and partial molecular response of 77%, 6% and 35% respectively.[50] In another study, a higher proportion of haematological responses were indeed observed in CALR-mutated ET treated after resistance or intolerance to HC.[51]

In the remaining patients without contraindications related to cardiac issues (e.g. arrhythmias, heart failure), anagrelide is considered a suitable option.[26] If anagrelide was used in the first line, peg-INF or HC is recommended. The choice will depend on the patient characteristics and the reason for the initial therapy.

In elderly patients or in those with a limited life expectancy, busulfan might be considered.[26] It has been shown to be an effective option for elderly ET patients who fail to receive HC. However, it is important to note that a significant rate of disease transformation was observed.[52] Therefore, busulfan could be considered in older patients due to intolerance, mainly leg ulcers, rather than resistance to HC.

Notably, although ET is associated with ageing, up to 15% of patients are younger than 40 years, and nearly 40% are younger than 60 years.[53] As peg-INF is the preferred initial drug for these patients, it may be replaced by HC or anagrelide.[26] It is worth noting that up to 10% of patients may discontinue peg-INF due to side effects.[40]

MANAGEMENT OF ET PATIENTS WITH *CALR* MUTATIONS

Compared to patients with *JAK2*V617F-mutated ET, those with *CALR* mutations tend to exhibit higher platelet counts, a lower risk of thrombosis and a higher risk of progression to secondary MF.[54] Moreover, the effectiveness and toxicity of cytoreductive and anti-platelet treatments differ depending on the molecular genotype. Thus, the PT1 study reported that *JAK2*V617F-negative patients are less sensitive to HC and require higher doses to achieve platelet control.[12] A recent study by the GEMFIN group included 1446 patients with ET, 267 of whom had the *CALR* mutation. In comparison with *JAK2*V617-mutated ET, *CALR*-mutated patients required a longer time to achieve response and had lower rates of complete haematological responses at 12 months, a shorter response duration and a higher frequency of resistance/intolerance to HC.[53]

Studies evaluating available cytoreductive agents in *CALR*-mutated ET showed similar efficacy for HC and anagrelide, with a rate of complete haematological response ranging from 36% to 56%[55–57] whereas peg-IFN seems to be more active, showing a complete haematological response in up to 77% of the cases.[13,51,58]

A consensus-based proposal from the European LeukemiaNet on the management of *CALR*-mutated ET has recently been published.[54] Based on these recommendations, our personal approach to the treatment of *CALR*-mutated ET is shown in Table 5.

MANAGEMENT OF *MPL*-MUTATED ET

MPL-mutated and *CALR*-mutated ET share clinical and histological characteristics, with both genotypes showing higher platelet counts and a marked megakaryocytic proliferation in comparison with *JAK2*V617F-mutated ET.[7,59–62]

TABLE 5 Personal management of *CALR*-mutated essential thrombocythaemia according to clinical characteristics.

	Clinical characteristics			
	History of thrombosis	Age >60 years or history of bleeding, or platelet count >1500 × 10^9/l	Age < 60 years, no risk factors	
			Symptomatic	Asymptomatic
Low-dose aspirin (ASA)	Yes[a]	No	Preferred over cytoreduction if platelet count <1000 × 10^9/l	No
Cytoreduction	Yes	Yes	Preferred over ASA if platelet count >1000 × 10^9/l	No
Modality	HC, ANA or Peg-INF	HC or ANA	Peg-INF	—
Platelet objective	Normalization of platelet count is recommended; however, if this approach results in toxicity, a lower intensity threshold might be appropriate, especially in patients without previous thrombosis or bleeding history			—

Note: Adapted from a ELN consensus-based proposal.[54]

Abbreviations: ANA, anagrelide; HC, hydroxycarbamide; Peg-IN, pegylated interferon.

[a]Anticoagulation if venous thrombosis.

These features might be explained because both *CALR* and *MPL* mutations result in selective MPL activation, which increases megakaryocytic proliferation. Some authors have reported a higher probability of MF progression and death in *MPL*-mutated ET, whereas contradictory results have been reported regarding thrombosis.[7,22,63–65] These discrepancies might be related to a confounding factor due to the older age of *MPL*-mutated patients. Moreover, a study including 1321 patients with ET characterized by next-generation sequencing (NGS) showed additional mutations in more than 50% of 60 cases, with *MPL*-mutated ET being the genotype with the highest proportion of additional mutations and clearly associated with older age.[23] The same study showed no increased risk of MF transformation in patients with an isolated *MPL* mutation.[23]

Due to its low frequency, there is scarce information regarding therapy for *MPL*-mutated ET. No studies have evaluated the efficacy of anti-platelet therapy in this genotype, and only one has assessed the haematological response to conventional cytoreduction, with a cumulative response rate of only 38% at 12 months and a high rate of resistance/intolerance to HC.[53] These results were comparable to those observed in *CALR*-mutated ET. Currently, there are no specific guidelines for MPL-mutated ET. In the meantime, based on common pathophysiological mechanisms, we recommend the same approach used for CALR-mutated ET.

MANAGEMENT OF TRIPLE-NEGATIVE ET

As stated in the current WHO/International Consensus classification, NGS studies are essential for the correct characterization of triple-negative ET since a proportion of these patients should be reclassified as *JAK2*-mutated or *MPL*-mutated but not detected by conventional techniques due to low allele burden or the presence of non-canonical variants.[66–71] The remaining patients might be classified as ET with high-risk mutations (see below), ET with other driver mutation (mainly TET2 or DNMT3A) or ET with no known mutation (Table 2).

Triple-negative ET has been classically associated with low thrombotic risk and longer survival.[72–74] As in *MPL*-mutated ET, there are no clear recommendations for the treatment of triple-negative patients. Patients with no known mutation mainly correspond to very low- or intermediate-risk categories of revised IPSET-thrombosis, and most of them may be managed with careful observation. Mutations in *TET2* and *DNMT3A* have been associated with an increased risk of arterial thrombosis, both in the general population[75–77] and in MPN.[78–80] Taking into consideration the lack of specific information regarding *TET2*$^+$/*DNMT3A*$^+$ triple-negative ET, it seems prudent to adopt a strategy aimed at the prevention of arterial thrombosis that includes anti-platelet therapy in the young, cytoreduction in patients older than 60 years and adequate control of CVRF for all of them.

MANAGEMENT OF ET PATIENTS WITH HIGH-RISK MUTATIONS

A minority of ET patients (< 2%) carry *TP53* mutations[23] with this frequency being higher in HC-resistant patients, as reported in 6.4% of patients included in the MAJIC trial.[81] ET with the *TP53* mutation is associated with shorter survival (median 13.8 years) due to disease progression to MF and acute leukaemia.

ET with mutations in spliceosome/chromatin genes including *EZH2, IDH1, IDH2, ASXL1, PHF6, CUX1, ZRSR2, SRSF2, U2AF1, KRAS, NRAS, GNAS, CBL, Chr7/7qLOH, Chr4qLOH, RUNX1, SF3B1, STAG2* and *BCOR* has been detected in 8% of the patients. These mutations have been associated in several studies with an increased risk of progression to MF and shorter survival, with one study reporting a median survival of 12 years.[23,82] Another study showed that resistance to HC, especially the development of cytopenia, was more frequently observed in patients with mutations in the *SRSF2, IDH1, IDH2* or *RUNX1* genes.[82]

In the absence of specific therapy, these patients are conventionally managed like other ET patients. With the incorporation of NGS into routine clinical practice, high-molecular-risk patients will be identified more frequently. These patients are candidates for close clinical and molecular follow-up to detect progression early. In this subgroup, new therapy is clearly needed due to the high rate of resistance to conventional agents and the increased risk of progression.

PREGNANCY

For young women wishing for pregnancy or already pregnant, the current treatment recommendations involve prescribing once-daily aspirin for those with 'very low-risk' or 'low-risk' conditions and pegylated IFN-α for those with high-risk conditions. Both aspirin and IFN-α therapies have been demonstrated to be safe during pregnancy and could reduce the risk of miscarriage. The routine use of low-molecular-weight heparin (LMWH) is recommended during fertility treatments and in case of subsequent pregnancy.[11,83] In patients with previous venous or arterial thromboembolism, the additional use of LMWH should be considered.[84] Interested readers can find specific pregnancy management guidelines elsewhere in this journal.[85]

NEW DRUGS FOR ET

Ruxolitinib

In PV, two phase 3 trials (the RESPONSE studies) reported the efficacy of this JAK1/JAK2 inhibitor in the treatment of PV patients with resistance to or intolerance to HC, leading to its second-line approval. In ET, a phase 2 trial involving 110 patients resistant/intolerant to HC (the MAJIC-ET study) did not demonstrate the superiority of

ruxolitinib over the best available therapy (BAT).[81] While ruxolitinib improved some disease-specific symptoms, there were no significant differences in the rates of thrombosis, bleeding or disease transformation.[81] Another phase 2 trial (RESET 272), also in the second line, is currently comparing ruxolitinib with anagrelide (NCT03123588).[11] Finally, the phase 2b RuxoBEAT trial compared first-line Ruxolitinib versus BAT in patients with high-risk ET. Preliminary results reported recently are consistent with those of the MAJIC-ET. Ruxolitinib was more effective in controlling symptoms and reducing spleen size, but not in achieving complete responses.[86]

Bomedemstat

Bomedemstat (IMG-7289) is an inhibitor of lysine-specific demethylase1 (LSD1). LSD1, is involved in the differentiation of megakaryocytic-erythroid progenitors into mature megakaryocytes, and loss of its activity is associated with loss of the self-renewal capacity of leukaemic stem cells.[87] Bomedemstat induces cell cycle arrest and apoptosis of *JAK2*V617F-mutated cells, resulting in a reduction in bone fibrosis, driver mutation allele burden and disease-associated symptoms. Bomedemstat is given orally, once a day (0.6 mg/kg/day), and the dose is adjusted depending on haemoglobin and platelet values. Preliminary results of an ongoing trial (IMG-7289-CTP-201) in ET patients, who have failed at least one prior line of treatment, have recently been reported.[88] These results indicate that bomedemstat is well tolerated, with most adverse effects being of grade 1–2 (in 30% of patients), and only 14% of patients requiring drug discontinuation due to adverse effects. In terms of efficacy, bomedemstat normalized platelet counts in 100% of the patients evaluated, decreased leucocytosis without inducing neutropenia and maintained stable haemoglobin values. It induced a significant improvement in symptoms, especially fatigue. At the molecular level, 67% of patients had a decrease in allele load regardless of the mutated driver gene (*JAK2, CALR or MPL*), with homozygous mutated cells being particularly sensitive to this decrease.[88] These positive results have contributed to the launch of a randomized clinical trial comparing bomedemstat and the best available therapy in HC-resistant/intolerant patients with ET.

Ropeginterferon

Ropeginterferon alfa-2b, a novel monopegylated interferon, is currently the only interferon authorized as a cytoreductive treatment in MPN, specifically in PV. The randomized, open-label phase 3 PROUD-PV trial and its extension phase CONTINUATION-PV compared ropeginterferon alfa-2b with HC in the first year (PROUD-PV trial), and up to 3 years with the best available treatment (BAT). This research provides evidence that, in PV, ropeginterferon alfa-2b is more effective in achieving durable haematological and molecular remissions than standard cytoreductive therapy.[24,89] A phase 3, multicentre, randomized, controlled SURPASS-ET trial (NCT04285086) comparing ropeginterferon alfa-2b with anagrelide in ET patients resistant or intolerant to HC is currently ongoing.[49]

Imetelstat

Imetelstat, a once-weekly intravenous telomerase inhibitor, demonstrated a complete haematological response rate of 89% in a phase 2 clinical trial involving 18 patients with ET who were refractory or intolerant to prior therapy. Significant molecular responses were observed within 3–6 months of treatment in 81% of patients with driver mutations in *JAK2*, *CALR* and *MPL*.[90] Further analysis evaluated the dynamics of mutations in additional myeloid genes, which were present in 50% of patients (*ASXL1, CBL, DNMT3A, EZH2, IDH1, SF3B1, TET2, TP53* and *U2AF1*). Most clones were reduced in parallel to the MPN driver mutation, including high-risk mutations (*ASXL1*, EZH2 and *U2AF1*), whereas mutations in *SF3B1* and *TP53* were associated with poor molecular response. In a minority of patients ($n = 3$), new mutations emerged during treatment (*TP53*, *IDH1* and *TET2*).[91] With a median time of 17 months (range 7–32 months), only 10 of the 18 patients (55%) continued treatment. The most frequent grade 3 or 4 side effects were neutropenia (22% of patients), anaemia, headache and syncope (11% of patients).[90] To our knowledge, further development of this drug in phase 2 and 3 ongoing clinical trials does not include patients with ET, but focus on more aggressive myeloid malignancies (MF, MDS or AML refractory/intolerant/relapsed to hypomethylating agents).[92]

IMMUNOTHERAPIES

The mutated calreticulin protein loses its anchoring capacity in the endoplasmic reticulum and is externalized, along with the trombopoietin receptor (TPO-R), on the cell surface. All mutant CALR proteins exhibit a tumour neoantigen located at the C-terminus that might open the possibility for developing targeted therapies (monoclonal antibodies, bispecific antibodies, vaccines and CART). Recently, a monoclonal antibody (INCA033989) has been developed to selectively antagonize the oncogenic function of mutated calreticulin. INCA033989, a humanized IgG1 antibody, selectively binds to mutated CALR and normalizes TPO-R downstream signalling in patient-derived haematopoietic stem cells and in an in vivo model of MPN.[93] In such a murine model, INCA033989 selectively reduced the levels of mutated CALR platelets and restored normal megakaryopoiesis while preserving bone marrow cellularity and the proliferation and differentiation capacity of

haematopoietic progenitors not carrying the *CALR* mutation.[93] The potential advantage of this antibody is that it acts at the stem cell and haematopoietic progenitor level, avoiding indiscriminate inhibition of the JAK–STAT pathway in non-mutated cells. Phase 1 trials have been initiated.

In a phase 1 trial, 10 *CALR*-mutated MPN patients (4 of them with ET) received 15 vaccines over 1 year with the CALRLong36 peptide derived from the *CALR* exon 9 mutations. Four of them had an in vivo IFN-g ELISPOT response at baseline, and four additional patients developed a response after vaccination. However, no clinical or molecular response was observed in any of the patients, suggesting that other therapeutic modalities (e.g. immune checkpoint inhibitors) should be used in combination with vaccines to enhance the anti-tumour immune response.[94]

CONCLUSION

Over the past two decades, there have been significant advances in the understanding of the pathogenesis of MPN, including ET. The discovery of *JAK2*/*CALR*/*MPL* mutations (i.e. the MPN driver mutations) has paved the way for targeted therapies. The outcome of well-designed randomized studies, involving conventional cytoreductive treatments and the novel agents currently under development, will help us to determine whether the latter are superior, acting not only as haematological response inducers but also as 'disease modifiers'. Meanwhile, we advocate for a more personalized treatment approach for ET, in which the incorporation of NGS studies plays a key role. This approach considers the well-established risk factors for both thrombosis and haemorrhage, along with the implications of molecular subtypes in shaping the disease's clinical course and response to current therapies.

AUTHOR CONTRIBUTIONS

Francisca Ferrer-Marín conceptualized the manuscript, reviewed the literature and wrote the first draft of the manuscript. Juan Carlos Hernández-Boluda reviewed and critically edited the manuscript. Alberto Alvarez-Larrán reviewed the literature, edited and finalized the final draft of the paper. All authors approved the final manuscript draft.

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CONFLICT OF INTEREST STATEMENT

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