Low-Risk Essential Thrombocythemia: A Comprehensive Review

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Abstract
Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm characterized by a persistently elevated platelet count in the absence of a secondary cause. The clinical consequences of uncontrolled thrombocytosis can include both thrombosis and hemorrhage. Patients with features conferring a "high risk" of vascular events benefit from reduction of the platelet count through cytoreductive therapy. The management of patients who lack such high-risk features has until recently been less well defined, but it is now apparent that many require minimal or even no intervention. In this review, we discuss the diagnostic pathway for younger patients with unexplained thrombocytosis, including screening molecular investigations, the role of bone marrow biopsy, and investigations in those patients negative for the classic myeloproliferative neoplasm driver mutations (*JAK2, CALR, MPL*). We discuss conventional and novel risk stratification methods in essential thrombocythemia and how these can be best applied in clinical practice, particularly in the era of more comprehensive genomic testing. The treatment approach for "low risk" patients is discussed including antiplatelets and the options for cytoreductive therapy, if indicated, together with areas of clinical need for future study.

Introduction

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm (MPN) characterized by an elevated platelet count. Together with polycythemia vera (PV) and primary myelofibrosis (PMF), these 3 conditions make up the classical Philadelphia chromosome-negative MPNs, which share common clinical features and shared molecular origins. ET has the most favorable prognosis of these disorders but presents considerable clinical heterogeneity, and the minority of patients who develop progression to myelofibrosis or acute myeloid leukemia have a much poorer outlook.

Diagnosis of ET is made on the basis of proliferative changes in the bone marrow, most marked within the megakaryocytic lineage, and either demonstration of clonality and/or the absence of a clear secondary cause for a thrombocytosis. There are subtle differences between the British Society of Haematology (BSH) 2014 diagnostic criteria[1] and the World Health Organization (WHO) 2016 diagnostic criteria[2] (Table 1), an important distinction being that a bone marrow biopsy is not necessary (although recommended) for a diagnosis of ET by the BSH criteria with an appropriate pathogenic mutation and the absence of any alternative myeloid malignancy being sufficient. A second difference is in the interpretation of reticulin fibrosis, with the WHO criteria regarding any increase in reticulin fibers (even WHO grade 1) as a rare feature in ET.

Risk Stratification: Defining "Low Risk" Disease

Vascular complications including arterial and venous thrombosis are the primary cause of morbidity and mortality in ET.[3,4] Thrombosis can be the presenting complaint leading to a diagnosis of ET, although many patients are now identified incidentally following blood counts performed for other reasons. The estimated incidence of thrombosis in ET is estimated to be around 14% at 10 years,[5] with prevalence at diagnosis of 10%-35%.[6,7] Microvascular complications are also observed, with symptoms including erythromelalgia, migraine, and paraesthesia.[6] Paradoxical bleeding episodes may occur, particularly in cases with extreme thrombocytosis (eg, platelet count >1000 × 10^9/L). Bleeding is typically due to an acquired von Willebrand syndrome (aVWS), the mechanism of which is not entirely clear but has been hypothesized to be due to the loss of high molecular weight multimers of von Willebrand factor (vWF) through increased proteolysis by ADAMTS13 and/or increased vWF adsorption onto the surface of platelets,[8,9] and appears to be platelet count-dependent.

Because thromboembolic events are the primary preventable cause of morbidity and mortality in ET, conventional risk stratification methods are built around differentiating between patients at higher and lower thrombotic risk. Age >60 years has consistently been shown to be associated with increased vascular risk.[7,10–13] Prior thromboembolic disease has also been found to be a strong predictor of subsequent vascular events.[10,11,13] Conventional risk stratification for ET comprises a 2-tier system where patients are described as high risk (age >60 years and/or history of thrombosis) or low risk (absence of either high-risk feature) and is derived from study by Cortelazzo et al,[10] with cytoreductive therapy traditionally reserved for high-risk patients.[14,15]

Diagnostic Criteria for Essential Thrombocythemia According to the BSH and WHO.

BSH (2014 Modification of 2010 Criteria)[1]		WHO 2016[2]	
A1	Sustained platelet count $\geq 450 \times 10^9$/L	Major criteria	Platelet count $\geq 450 \times 10^9$/L
A2	Presence of an acquired pathogenic mutation (JAK2/CALR/MPL)		BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
A3	No other myeloid malignancy		Not meeting WHO criteria for BCR-ABL1 + CML, PV, PMF, MDS, or other myeloid neoplasms
A4	No reactive cause for thrombocytosis and normal iron stores		Presence of JAK2, CALR, or MPL mutation
A5	Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm. Reticulin is generally not increased (grades 0–2/4 or grade 0/3)	Minor criteria	Presence of a clonal marker (eg, abnormal karyotype) or absence of evidence for reactive thrombocytosis
Diagnosis requires A1-A3 or A1 + A3-A5		Diagnosis requires all 4 major, or first 3 major and one minor criteria	

BM = bone marrow; BSH = British Society of Haematology; CML = chronic myeloid leukemia; MDS = myelodysplastic syndrome; PMF = primary myelofibrosis; PV = polycythemia vera; WHO = World Health Organization.

The primary thrombocythaemia-1 (PT1) study was an international trial investigating treatment optimization for different risk groups in ET. "High"-risk patients were defined as those over the age of 60, with a previous marked thrombocytosis (>1000 or 1500×10^9/L depending on date of trial entry), history of ischemia, thrombosis or embolic events, hemorrhage related to ET or the presence of hypertension or diabetes requiring medication. "Low" and "intermediate" risk patients lacked high-risk features and were aged 18-39 years old or 40-59 years old, respectively. Given that the vascular risk of intermediate-risk patients was not reduced by the addition of cytoreductive therapy to aspirin, there does not appear to be additional utility from separating low- and intermediate-risk groups in this manner.[16]

The presence of the *JAK2 V617F* mutation has been shown to independently increase the risk of vascular events in ET.[7,13,17–19] Following the identification of this mutation and other putative risk factors for thrombosis including a raised white cell count, a retrospective multivariable analysis incorporated a number of factors into a single prognostic score for thrombosis, the International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis).[20] This model delineated patients into 3 risk groups according to an age >60 years (1 point), cardiovascular risk factors including tobacco use, hypertension, and diabetes mellitus (1 point), previous thrombosis (2 points), and *JAK2 V617F* positivity (2 points). Patients with <2 points could be considered low risk (thrombosis risk 1.03% of patients per year), 2 points intermediate risk (thrombosis risk 2.35% of patients per year), or >2 points high risk (thrombosis risk 3.56% of patients per year). A revised IPSET-thrombosis score was subsequently devised through re-analysis of the original dataset, leading to a 4-tier model where patients were classified as very low risk (no thrombosis, age <60, *JAK2* unmutated), low risk (no thrombosis, age <60, *JAK2* mutated), intermediate risk (no thrombosis, age > 60, *JAK2* unmutated), and high risk (thrombosis history; or age >60 and *JAK2* mutated)[21]; cardiovascular risk factors were no longer a part of the model. The revised IPSET-thrombosis score has been validated by Haider et al[22] and its use has been adopted by both European LeukaemiaNet and National Comprehensive Cancer Network guidelines,[15,23] although there remains a lack of prospective clinical trials of ET management using this classification.

Other risk factors explored in the context of thrombosis in ET include an increased white blood cell count, splenomegaly, aquagenic pruritus, and an elevated red cell distribution width.[7,13,24–29] None of these are widely used in risk stratification, although leukocytosis has been reproducibly shown to be a thrombotic risk factor, albeit with potential confounding factors including smoking and *JAK2 V617F* status, both of which are associated with neutrophilia. Leukocytosis is not generally used in isolation for risk stratification but may be considered in conjunction with other clinical parameters in patients with an otherwise borderline risk status.

In the United Kingdom, the conventional 2-tier system remains the most widely used risk stratification method and for the purpose of this review, low-risk patients are considered as those <60 years old with no previous thrombosis or hemorrhage (secondary to ET). Patients with extreme thrombocytosis are at increased risk of major hemorrhage,[26] providing a rationale for also managing patients with extreme thrombocytosis (ie, a platelet count of >1500×10^9/L) with cytoreductive therapy, as per other "high-risk" patients.

Epidemiology and Genomics

Epidemiology and natural history

ET is a rare disease with an incidence of around 1-5 per 100,000[7,30–32] and a prevalence of 38-57 per 100,000 population.[33] In contrast to other MPNs, ET is more common in females.[33,34] It is primarily a disease of older age with a usual age of onset of 50-60 years, although there is also a substantial cohort of younger patients diagnosed with ET.[35] Overall survival is only mildly reduced when compared with the general population[30,36] and prognosis is more favorable in ET than in PV or PMF, regardless of molecular subtype.[37] Younger patients in particular appear to have a more indolent course with individuals <60 years old and with a platelet count of <1500×10^9/L noted to have a thrombotic risk comparable with that of the general population.[38] Overall survival is also better in younger patients, with a recent Mayo Clinic study estimating an overall survival of 35 years for those <40 years of age, compared with 22 years for those aged 41-60 and 11 years for those >60 years of age.[39] Age <60 years has been associated with a reduced rate of leukemic transformation and myelofibrosis when compared with those over the age of 60, although given the long survival of younger patients, the lifetime risks may be comparable.[5,40]

Genomics of ET and low-risk disease

Our understanding of the role of molecular genetics in the pathogenesis of myeloproliferative disorders came to the forefront with the discovery that an acquired point mutation (Val617Phe) in the gene encoding the tyrosine kinase

JAK2 was present in a significant proportion of patients with MPNs.[41–44] This mutation is associated with increased, constitutive JAK2 tyrosine kinase activity, and increased downstream signaling through hematopoietic growth factor pathways. Subsequent work has led to the identification of 2 additional key phenotypic driver mutations in ET and PMF: mutations in exon 10 of the thrombopoietin receptor gene (*MPL*)[45] and, more recently, mutations in exon 9 of the cal-reticulin gene (*CALR*).[46] Neither *MPL* nor *CALR* mutations are seen in PV.[37,45,46] All 3 mutations are considered mutually exclusive except in rare cases.

In ET, *JAK2 V617F* is the most common driver mutation, being found in around half of patients.[16,37,41,47] *CALR* mutations are found in between a quarter and a third of patients, whereas *MPL* mutations are the least common (~5%).[37,45–47] Around 10%-15% of patients are negative for all 3 mutations ("triple-negative" ET).[37,48] In younger patients, *JAK2* mutations are less frequent while *CALR* mutations are slightly commoner, as compared to the older population.[39] "Triple-negative" ET is also commoner in younger patients; for example, 1 study reported a frequency of 16% in patients <40 years of age compared with 8% in those >60 years of age.[39]

Next-generation sequencing panel assays have recently been used to pursue more comprehensive genomic analysis in MPNs and have further clarified the molecular etiology of triple-negative disease. In a study of 2035 patients with MPNs, of whom 1321 (almost two-thirds) had ET, analysis for recurrent aberrations of 69 genes and genome-wide copy number in myeloid malignancies was performed.[48] Of the patients with triple-negative ET, a minority showed an alternative driver mutation, including noncanonical mutations in *JAK2* and *MPL*. However, over 80% of these patients with ET had no detectable somatic mutations or chromosomal aberrations that are recurrent in myeloid malignancies (this compares to just over 40% with PMF). A lack of known driver mutations was particularly seen in younger patients, with no "'triple-negative" MPN patients <39 years of age having any detectable driver mutations and <10% of those aged 39-57 having a detectable driver lesion.

This triple-negative group is particularly pertinent to a discussion of low-risk ET because these patients are over-represented in younger cohorts. The natural history of this subgroup is also important. Setting aside conventional diagnostic classifications, Grinfeld et al's[48] article used Bayesian clustering to divide the whole MPN cohort into 8 genomic subgroups, with those described as ET falling most often into the subgroup with a heterozygous *JAK2* mutation, followed by the subgroup with a *CALR* mutation, and next the subgroup with a chromatin or spliceosome mutation. Small minorities of ET patients showed a *MPL* mutation, *TP53* aberration or homozygous *JAK2/NFE2* mutation. For the final subgroup of interest, those with no known driver mutation, when the underlying diagnosis was ET, there was a very low transformation rate and overall survival was significantly better than that of MPN patients with a heterozygous *JAK2* mutation. These findings are in keeping with more selective, small studies of young MPN patient cohorts, in which a high prevalence of triple-negative disease is reported, together with low rates of thrombosis and transformation.[49]

It is therefore apparent that we have a very limited understanding of disease etiology in many patients with triple-negative ET, but it may represent a biologically distinct entity with its own natural history. A proportion of such patients may have a nonclonal and/or reactive disorder. It is also notable that in a young patient with triple-negative disease, most patients who are investigated with the new "gene panel" sequencing assays will have a negative test, although a broad panel that includes full coding regions of *JAK2* and *MPL* will be informative in a minority.

Genomics and risk stratification

JAK2 V617F has been consistently associated with increased thrombotic risk in ET, as discussed above. *JAK2 V617F* mutant allele burden in peripheral blood has also been shown to correlate with an increased risk of thrombosis in some MPN studies,[50–52] although high allele burdens are more commonly seen in PV and PMF than in ET.[53,54] Patients with *CALR* mutations, but also "triple-negative" cases, show consistently lower rates of thrombosis when compared with those with *JAK2 V617F* mutations, suggesting that presence or absence of a *JAK2* mutation, rather than *CALR*, is the key factor influencing risk.[55,56] Prothrombotic effects of *JAK2 V617F* are also supported by the identification of the mutation in individuals with splanchnic vein thrombosis and apparently normal blood counts and by preclinical studies of platelet, leukocyte, and endothelial cell biology in the context of *JAK2 V617F*.[57–60] The presence or absence of mutated *CALR* had no effect on risk stratification using the IPSET-thrombosis model.[61] The role of *MPL* mutations in thrombosis is unclear, given that such patients are found less frequently, although some studies have suggested a comparable thrombotic rate to those with mutated *JAK2*.[55,62]

For other long-term disease outcomes, studies of the 3 major molecular subgroups (*JAK2*, *CALR*, *MPL*) have mostly not identified clear differences in overall survival or transformation-free survival, although patients with *MPL* mutations showed an increased rate of myelofibrotic transformation in 1 study.[62] Subsequent studies have investigated the prognostic significance of other recurrent mutations. For example, Tefferi et al[63] showed that mutations in *SH2B3*, *SF3B1*, *U2AF1*, *TP53*, *IDH2*, and *EZH2* were associated with less favorable outcomes in ET. More recently, these authors proposed a prognostic model for ET (Mutation-enhanced International Prognostic Systems) which seeks to incorporate the presence or absence of specific adverse mutations (*SRSF2*, *SF3B1*, *U2AF1*, and *TP53*), noting that patients who harbor one or more of these mutations have an increased rate of progression to acute leukemia and myelofibrosis, and poorer overall survival.[64] Patients were scored according to the presence of leukocyte count >11 × 10^9/L (1 point), male gender (1 point), adverse genetics (2 points), and age >60 (4 points) and stratified into 3 groups: low risk (0-1 points), medium risk (2-5 points), or high risk (6 or more points), with a median overall survival of 34.4, 14.1, and 7.9 years, respectively.

As described above, Grinfeld et al's[48] study of comprehensive genomic profiling demonstrated that patients with ET and no identifiable myeloid driver mutation showed favorable outcomes. This study also used data from the whole cohort of 2035 patients to generate a multivariable, multistate prognostic model, through which the genomic profile from an individual patient can be used to generate personally tailored prognostic predictions, including risks of disease transformation to leukemia or myelofibrosis and overall survival. This approach integrates more comprehensive clinical and available genomic information to provide an individualized estimate of risk. In general, this offers advantages over alternative methods that segregate patients into discrete risk categories that may have widely different median survival estimates,[65] and where a patient's estimated prognosis may change considerably when, for example, they reach a particular birthday.

Diagnostic Work-up in Low-Risk ET

Figure 1 shows our standard diagnostic practice for thrombocytosis in a patient <60 without previous vascular events. We recommend a bone marrow biopsy in all low-risk patients, even though some diagnostic criteria (BSH, Table 1) allow a diagnosis of ET to be made in patients with persistent thrombocytosis and a confirmed mutation in *JAK2*, *CALR*, or *MPL* if other myeloid
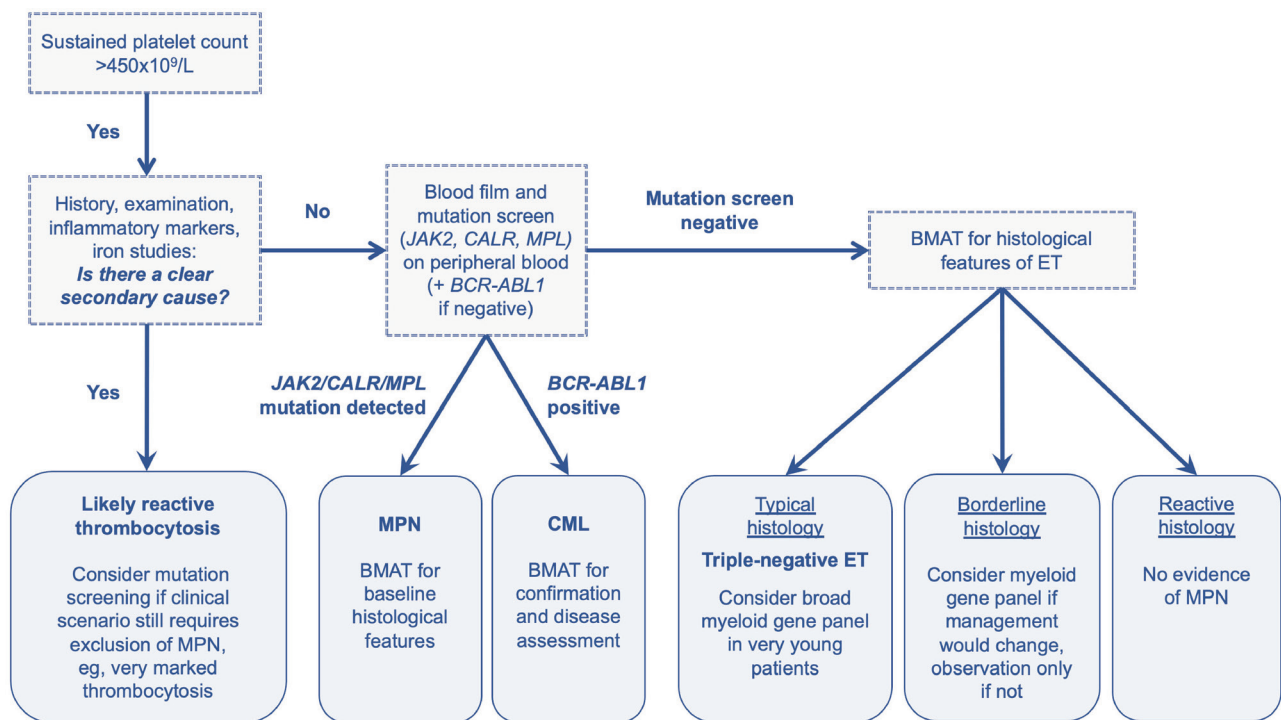
Figure 1. Diagnostic pathway for essential thrombocythemia. BM = bone marrow; BMAT = bone marrow aspirate and trephine; CML = chronic myeloid leukemia; ET = essential thrombocythemia; MPN = myeloproliferative neoplasm.

malignancies are excluded on clinical and laboratory assessment. Where WHO criteria (Table 1) are used for diagnosis, bone marrow examination is mandatory and allows a distinction to be made from the entity of prefibrotic myelofibrosis. It is useful to record a baseline assessment of reticulin grade in the event of future suspected disease transformation, given the potentially long disease course ahead. In patients in whom there are unusual clinical features at presentation, bone marrow examination should be used to seek atypical histological features that may overlap with other disease entities. Examples include patients with prominent splenomegaly or constitutional symptoms, borderline hemoglobin levels or cytopenias, or a leukoerythroblastic blood film. Splanchnic vein thrombosis and associated portal hypertension are often associated with plasma volume expansion that may mask elevated red cell mass,[66] and marrow appearances may more closely resemble PV even in the absence of a raised hematocrit, but these patients are by definition not low risk.

Which patients with low-risk ET and a *JAK2, CALR,* or *MPL* mutation should undergo comprehensive genomic profiling, typically with targeted sequencing of a panel of "myeloid" genes? In our practice, such analysis is performed infrequently, but would be considered in specific groups: (1) Patients with atypical clinical or histological features, such as marked splenomegaly, including those seen more typically in myelofibrosis but without meeting full diagnostic criteria; (2) Patients who develop features during the course of disease such as cytopenias and morphological dysplasia, where the distinction between effects of therapy and transformation is challenging; (3) Patients for whom there are grounds to attempt an individualized prediction of prognosis, such as that provided by the Sanger multistate model[48]; (4) When required as part a clinical trial.

In patients with unexplained, persistent, and significant thrombocytosis in whom *JAK2, CALR,* and *MPL* mutation and *BCR-ABL1* fusion screening on peripheral blood are negative, bone marrow examination is also essential and can be conclusive in distinguishing from a reactive etiology (Figure 2). It is worth noting

however that since the identification of all 3 phenotypic driver mutations, the utility and reproducibility of histological diagnostic criteria have not been confirmed specifically in "'triple-negative" cases. There can be substantial interobserver variability in the interpretation of WHO histological criteria for MPNs including ET.[67] Classical histological features of ET have been reported in a small case series of pediatric triple-negative ET, but the median presenting platelet count was very high (1251×10^9/L for the whole pediatric ET cohort studied).[68] In some patients with mild or moderate thrombocytosis and no confirmatory molecular marker, a confident histological diagnosis can remain challenging, even for an expert hematopathologist. Although rare, the possibility of hereditary thrombocytosis should also be considered in young patients with an otherwise unexplained thrombocytosis and no previous demonstration of a normal platelet count. These conditions may involve germline mutations in the gene responsible for thrombopoietin production, *THPO*. Germline mutations in *MPL* and *JAK2* have also been implicated in hereditary thrombocytosis but are not restricted to the classical exon 10 (*MPL*) and V617F (*JAK2*) mutations associated with ET.[69]

For triple-negative patients, we do not repeat *JAK2 V617F* analysis on bone marrow aspirate following a negative test on peripheral blood DNA, since mutant allele burdens are usually similar between such paired samples.[70] Equivalent data are lacking for *CALR* and *MPL* mutations and if bone marrow histology is suggestive of an MPN, we repeat these analyses on bone marrow. Should all patients under investigation for "triple-negative" thrombocytosis undergo more comprehensive myeloid gene panel testing? As noted above, a minority of such patients may be found to harbor a mutation, providing helpful information if positive, but diagnostic yield will depend on panel content and will be particularly low in young patients.[48] We would consider gene panel studies: (1) In young patients with bone marrow histology typical of ET, where confirmation of a clonal disorder is useful in view of the patient's likely long-term disease course, but ideally where a broad panel that covers noncanonical variants
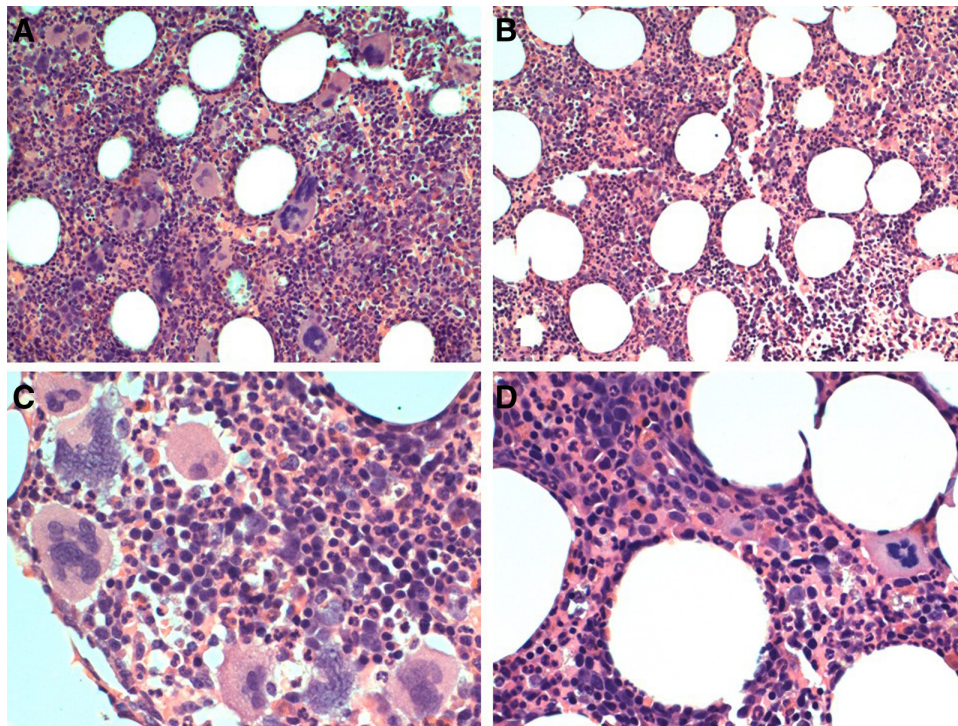
Figure 2. Bone marrow histology in triple-negative essential thrombocythemia and reactive thrombocytosis. A and B: A bone marrow trephine biopsy from a 30-y-old woman with an isolated thrombocytosis of 1300-1400 × 10⁹/L, no apparent secondary cause and no *JAK2*, *CALR*, or *MPL* mutation on standard screening assays. Histology shows a mildly hypercellular marrow, increased megakaryocytes with large, atypical forms and some clusters, in keeping with triple-negative essential thrombocythemia. C and D: A biopsy from a 35-y-old woman with an isolated thrombocytosis of 800-900 × 10⁹/L on a background of Crohn's disease and rheumatoid arthritis, with negative molecular screening. Histology shows a mildly hypercellular marrow with minimal megakaryocyte hyperplasia and without proliferative morphology, in keeping with a reactive thrombocytosis.

in *JAK2* and *MPL* and a range of other driver genes is available; (2) In patients with significant thrombocytosis (eg, >600 × 10⁹/L) with no reactive cause and borderline bone marrow histology, where cytoreduction would be indicated if there is evidence of a clonal disorder, such as in those with an unexplained thrombotic event. Altogether patients with suspected low risk, triple-negative ET can present a diagnostic challenge and a formal multi-disciplinary discussion including clinical and pathology teams is particularly valuable to consider all aspects of a case, including any potential reactive cause. Where there is inadequate information to make a definitive diagnosis, a period of observation without therapy is often a safe and pragmatic approach.

Treatment of ET

Antiplatelets

Aspirin is an antiplatelet agent used widely in doses of 75-100 mg daily to reduce thrombotic risk in MPNs, as well as providing symptomatic benefit for microvascular complications such as erythromelalgia.[71] The previous widespread recommendation for the use of low-dose aspirin in ET was an extrapolation from PV, in which a randomized placebo-controlled trial showed a reduced risk of thrombosis without an increase in bleeding.[72] There are no equivalent prospective data in ET, which has a more heterogeneous molecular pathogenesis. A retrospective, observational study looking at aspirin use in low-risk ET found a lower rate of thrombosis in *JAK2 V617F*-mutated ET in those taking aspirin compared to those taking no aspirin, with no effect on bleeding risk.[73] In those with a *CALR* mutation, however, there was no difference in thrombotic rate between the groups and bleeding events were higher in those taking aspirin. There are some limitations of the study, in particular

its retrospective nature, although a very large, prospective randomized trial with a long duration of follow-up and without crossover would be required for cleaner data. Nonetheless, the previous universal recommendation for aspirin in low-risk ET[14] now warrants reconsideration.

Our practice is to recommend aspirin in low-risk *JAK2*- and *MPL*-mutated ET. With a platelet count 1000-1500 × 10⁹/L, patients are counseled to monitor for increased bleeding or bruising but this occurs infrequently, and von Willebrand factor levels are checked in these circumstances. For patients with low-risk *CALR*-mutated ET, we advise patients of the paucity of evidence to guide practice and consider individuals on a case-by-case basis. We are more likely to consider aspirin with increasing age or with cardiovascular risk factors but would more often avoid antiplatelets in those with a platelet count over 1000 × 10⁹/L. Evidence is even more limited for histologically-confirmed triple-negative ET, for which our practice is similar to *CALR*-mutant disease. Aspirin is not recommended in any patient with an overt bleeding phenotype, including confirmed aVWS, although this might sometimes be reconsidered in the future, for example, following cytoreduction and normalization of vWF levels.

Some patients with ET have been hypothesized to develop a degree of aspirin resistance as a consequence of increased platelet turnover and cyclooxygenase-1 renewal.[74] It has previously been suggested that such aspirin resistance could be overcome by increasing the dosing interval to 75-100 mg twice daily.[75,76] Recently, the phase-2 Aspirin Regimens in Essential Thrombocythemia trial randomized 243 patients with ET between once-daily, twice-daily, and 3 times daily low-dose aspirin.[77] Measurement of thromboxane B2 levels indicated that the majority of patients on a once-daily aspirin regimen show suboptimal platelet inhibition. A twice-daily regimen significantly improved the degree of platelet inhibition and appeared well-tolerated. The 3 times daily regimen gave no additional benefits for

platelet inhibition, but was associated with higher rates of gastrointestinal discomfort. It has yet to be demonstrated whether improving the level of platelet inhibition has any effect on the rate of thrombotic or bleeding events, nor whether long-term tolerability will be equivalent.

Cytoreduction

Cytoreductive therapy reduces the rate of thrombosis in patients with ET and high-risk features,[78] but universal use of cytoreduction appears unnecessary. The intermediate-risk arm of the PT1 trial randomized patients aged 40-59 years and without high-risk features to hydroxycarbamide plus aspirin or aspirin alone.[16] After a median duration of follow-up of 73 months, addition of hydroxycarbamide neither reduced the incidence of vascular events nor the rate of progression to myelofibrosis or leukemia. As such, routine use of cytoreduction in patients without high-risk factors for thrombosis is not recommended. There are situations however where cytoreduction is considered. The most common is a rising platelet count, given the increased risk of hemorrhage with extreme thrombocytosis. A platelet count persistently exceeding 1500×10^9/L is often considered a trigger to commence cytoreduction,[15] although there are no prospective data to validate this specific threshold. Cytoreduction to a platelet count of less than 1000×10^9/L generally leads to a resolution of any bleeding diathesis and normalization of vWF ristocetin cofactor activity in patients who have an aVWS[8]; there is no evidence that achievement of a normal platelet count is necessary when the indication for cytoreduction was extreme thrombocytosis, especially if asymptomatic. Less common situations where cytoreduction may be considered in patients with low vascular risk include those with severe symptoms such as headaches. In this situation, the platelet count target can reflect the indication, that is, the goal is symptom control.

For patients with low-risk ET requiring cytoreduction, the options used most frequently are interferon-alfa, hydroxycarbamide, and anagrelide. Hydroxycarbamide is an antimetabolite medication, administered orally and generally well-tolerated with the commonest side effects, including myelosuppression, mild gastrointestinal upset, leg and mouth ulcers, and other skin reactions. In high-risk ET, the efficacy and safety of hydroxycarbamide as a first-line cytoreductive therapy are well established.[78,79] Hydroxycarbamide is potentially teratogenic and should be avoided in those who are pregnant or planning to conceive.[80] It is associated with an increased risk of non-melanoma skin cancers, although there is no clear evidence for an association with other nonhematological malignancies.[81] Concerns have been raised about a potential increased risk of leukemic transformation,[82,83] although this has never been confirmed in any well-controlled comparative clinical study.[84–86] Nonetheless, these potential issues remain of concern in a very young patient when considering therapy that may be taken indefinitely.

Alternatives to hydroxycarbamide include anagrelide, which had a higher incidence of treatment withdrawals due to side effects in the high-risk arm of the PT1 study.[79] It is often well-tolerated at lower doses and is sometimes used in combination with hydroxycarbamide, although the side-effects such as headaches and palpitations are more common with dose increases and it is not safe in pregnancy. It is not associated with increased risks of second malignancy,[81] which may make its use attractive in younger patients, but in the PT1 trial, it was associated with increased rates of arterial thrombosis, hemorrhage, and fibrotic progression compared to hydroxycarbamide,[79] so it is typically considered a second-line agent.[15]

Interferon-alfa has been used in MPN management for several decades, although its mode of administration (subcutaneous injection) and side effects such as "flu-like" symptoms and mood disturbance have been an issue. Efficacy of the pegylated form, which requires less frequent injection and is better tolerated, was demonstrated in phase 2 studies in ET and PV, including an 81% hematological response rate and 76% complete hematological response rate in ET.[87] Six of 16 patients with *JAK2 V617F*-mutated ET showed a molecular response, with one achieving a complete molecular response. Only 10% of patients discontinued treatment due to toxicity. More recently, the phase 2 Myeloproliferative Disorders - Research Consortium (MPD-RC)-111 study demonstrated hematological response rates of 69.2% in ET, with particularly high rates of complete response (56.5%) seen in *CALR*-mutated patients[88] and comparable discontinuation rates due to toxicity with earlier studies (13.9%). The phase 3 MPD-RC-112 trial randomized 168 patients with high-risk PV or ET to either pegylated interferon alfa or hydroxycarbamide. Preliminary data suggest comparable response rates between the 2 arms with a higher rate of grade 3/4 adverse events in the pegylated interferon-alfa arm, although final publication is awaited.[89,90] Ropeginterferon alfa-2b is a novel, long-acting interferon which in PV showed a favorable rate of complete hematological response at 36 months compared to hydroxycarbamide (71% versus 51%; P = .012), in the pegylated interferon alpha-2b versus hydroxyurea in polycythaemia vera and CONTINUATION-PV phase 3 trials.[91] Although this drug is now licensed for PV, its efficacy in ET has not yet been demonstrated in a randomized trial.

In summary, pegylated interferon-alfa appears effective and well tolerated in ET, with potential advantages over other therapies for younger patients requiring cytoreduction. Although molecular responses have been observed, it remains to be confirmed in ET whether these translate into reductions in rates of important long-term outcomes including thrombosis and disease transformation.

The JAK inhibitor ruxolitinib was compared with "best available therapy" in patients with ET who were resistant to or intolerant of hydroxycarbamide in the UK MAJIC-ET (A randomised study of best available therapy vs JAK inhibition in patients with high risk Polycythaemia Vera or Essential Thrombocythaemia who are resistant or intolerant to Hydroxycarbamide - ET arm) study.[92] There was no improvement in the primary endpoint of complete hematological response at a year in patients randomized to ruxolitinib. Other cytoreductive agents including busulfan and radioactive phosphorous are associated with increased rates of leukemic transformation and are not recommended in low-risk patients.[85,93,94]

Management of low-risk ET in pregnancy

MPNs in pregnancy are rare, with a reported incidence of 3.2/100,000 pregnancies, of which around 4 of 5 are in patients with ET.[95] The live birth rate in MPNs is reduced (71.1%), compared with an expected rate of around 80%.[96,97] Pregnancy in ET is associated with additional risk to both mother and fetus, including maternal thrombosis, pre-eclampsia, intrauterine growth retardation, and fetal loss[80,96] and patients considering pregnancy should be counseled accordingly.

The management of MPNs in pregnancy has been expertly summarized recently by Robinson and Harrison.[80] A multidisciplinary approach from obstetric, hematology and in some cases, anesthetic teams is essential from an early stage to reduce the risks to the patient. The authors have suggested that low-dose aspirin should be offered routinely to all ET patients throughout pregnancy unless there are specific contraindications (eg, aVWS), together with 6 weeks of thromboprophylaxis in the postnatal period. Antenatal thromboprophylaxis with low molecular weight heparin is offered to patients with an additional risk factor for venous thromboembolism. For low-risk patients who require cytoreduction for reasons discussed above, interferon-alpha is preferred.[14,80] Careful monitoring during pregnancy with regular full blood counts, blood pressure monitoring and urinalysis is recommended. Uterine artery Doppler

studies and serial fetal growth scans should be offered to identify those requiring more intensive monitoring and/or intervention.

Controversies in the Management of Low-Risk ET

Prefibrotic PMF

Prefibrotic PMF (pre-PMF) as defined by WHO 2016 criteria is a subgroup of PMF, characterized by megakaryocyte proliferation and morphological atypia but without significantly increased bone marrow fibrosis.[2] The bone marrow is characteristically hypercellular with granulocytic proliferation. Features comprising the "minor" diagnostic criteria, of which at least one is required, are splenomegaly, elevated lactate dehydrogenase, anemia, and leukocytosis. However, the clinical presentation can show substantial overlap with that of ET, some patients do not fit neatly into either category (receiving a WHO diagnosis of "MPN, unclassifiable"), and even experienced hematopathologists show variable interobserver reproducibility when interpreting the histological features to distinguish between ET and pre-PMF in routine practice.[67,98–100] It is reported that patients with pre-PMF have worse outcomes than those with ET, including shorter overall survival and higher rates of transformation to acute leukemia and overt PMF.[36,101] In practical terms, for many patients in whom the primary clinical presentation is of asymptomatic thrombocytosis without anemia, the distinction between the 2 conditions does not influence immediate management and in the absence of any vascular high-risk factors, therapy is usually as described above. The distinction between pre-PMF and ET is therefore at present largely prognostic, although features suggestive of pre-PMF on histology and/or the presence of some of the minor diagnostic criteria might at minimum prompt more comprehensive molecular studies at diagnosis in a younger patient, together with closer clinical surveillance.

Hematocrit in *JAK2 V617F*-mutated ET

A further point of diagnostic interest is differentiating between low-risk *JAK2*-mutated ET and PV. WHO and BSH diagnostic criteria use different blood count parameters and thresholds for the diagnosis of PV (eg, hematocrit of >0.49 for males or >0.48 for females per WHO, and >0.52 for males or >0.48 for females per BSH[2,102]); the rationale behind these criteria is discussed elsewhere.[102] The distinction between *JAK2 V617F*-mutated ET and PV appears to be influenced by a range of acquired and germline factors, some quantitative and others qualitative, including *JAK2 V617F* allele burden, gender, mutation order, and subclonal hierarchy (reviewed elsewhere[103]). In PV, there is evidence from the randomized cytoreductive therapy in PV (CYTO-PV) trial that managing hematocrit to a target of <0.45 (rather than <0.5) reduces vascular events,[104] whereas there is no evidence or widespread recommendation for controlling hematocrit in ET. A patient with *JAK2*-mutated ET would therefore not typically be treated for a high-normal hematocrit (eg, 0.46-0.47), even though this would be above the target threshold for venesection if the diagnosis were PV. This may seem counterintuitive given that these 2 diseases are often considered as 2 steps within a biological continuum.[17,103] In the CYTO-PV trial, the benefits of tighter hematocrit control appeared somewhat less convincing in younger patients, but the trial was not powered for such subgroup analyses and an interaction with age was not statistically significant. Studies of ET have not reported associations between red cell parameters and thrombotic risk,[26] although these would have been populations with mixed molecular etiology. Given the low thrombotic rate in low-risk ET, the lack of evidence supporting hematocrit control and the potential for morbidity and increasing

thrombocytosis due to iron deficiency, we do not routinely venesect patients with low-risk *JAK2*-mutated ET and a hematocrit >0.45. Progression to PV in patients with *JAK2*-mutated ET is well recognized; however,[17,105] and we observe patients with a rising hematocrit closely, instituting venesection once diagnostic criteria for PV are met. Patients with ET lacking a *JAK2* mutation do not typically progress to PV and a rising hematocrit should prompt consideration of alternative causes.

Conclusions

Current management of ET is based on conventional risk stratification methods that stratify by risk of vascular events. In low-risk ET, conventional therapy is centered on the use of low dose aspirin, for which a more evidence-based approach to delivery and dosing according to genomics and platelet count would be preferable. Cytoreduction does not afford additional protection against vascular events in patients lacking high-risk factors for thrombosis. For those low-risk patients who do require cytoreduction however (eg, for symptoms), a number of agents are available with pegylated interferons showing increasing promise in recent trials.

Conventional diagnostic and risk-stratification techniques were devised largely in the pregenomic era. We are increasingly aware that disease biology may be better reflected in new genomic classifications than in our conventional diagnostic systems based largely on histology. Similarly, newer risk stratification models are able to take such genomic factors into account and integrate them with traditional clinical risk factors, providing a more accurate and individualized prognosis and potentially opening the opportunity to target interventions to those with higher risk disease. Future studies will need to prospectively establish the place of these integrated prognostic models, in identifying patients whose disease is most likely to transform and who warrant earlier intervention including trials of novel therapeutic agents. By contrast triple-negative, low-risk disease remains a poorly characterized entity that warrants further biological study, but for which prognostic models can nonetheless provide the reassurance of predicted excellent outcomes in many patients.

Disclosures

The authors have no conflicts of interest to disclose.

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