How we treat essential thrombocythemia

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Abstract

The last five years have witnessed significant advances in both the diagnostic process and optimal therapy for patients with essential thrombocythemia (ET). Insights into the underlying molecular mechanisms have been accompanied by the development of new diagnostic tests and by an improved understanding of the relationship between ET and other related myeloproliferative neoplasms such as polycythemia vera (PV) and primary myelofibrosis (PMF). In the first part of this review, we describe how recent molecular and histological studies can be integrated into a streamlined diagnostic process which is applicable to everyday clinical practice. We also address areas of current diagnostic controversy, including heterogeneity within ET and the phenotypic overlap between ET, PV and PMF. In the second part, we provide an overview of our current approach to the treatment of ET including risk stratification, choice of cytoreductive agent and a consideration of special situations such as the pregnant or peri-operative patient. Areas of controversy discussed include the identification of those at high risk of complications and therapeutic decisions in the younger patient.
Introduction

Essential thrombocythemia (ET) is a clonal stem cell disorder which shares phenotypic and pathological similarities with other myeloproliferative neoplasms (MPN), particularly polycythemia vera (PV) and primary myelofibrosis (PMF). The last five years have seen an acceleration in our understanding of these disorders, following the identification of an acquired JAK2 V617F mutation in around 50% of ET patients, along with half of those with PMF and the vast majority with PV. Subsequently mutations in MPL were reported in around 4% of patients with ET or PMF, and mutations in TET2 have been observed in a variety of myeloid malignancies including JAK2 V617F-positive and negative ET. In this article, we explore the impact of recent molecular and therapeutic advances on the way we diagnose and manage patients with ET.

How we diagnose essential thrombocythemia

We consider a diagnosis of ET when there is an unexplained and persistent thrombocytosis (platelet count >450 x10^9/L). ET has traditionally been a diagnosis of exclusion, requiring the absence of reactive conditions and other clonal disorders that may present with thrombocytosis (Table 1). The discovery of mutations in JAK2 and MPL now allows for the positive identification of ET in over a half of all cases. In our practice, screening for the JAK2 V617F mutation is the initial investigation performed in all patients with suspected ET, followed by screening for MPL exon 10 mutations in V617F-negative cases. TET2 screening is not currently performed as mutations are present in a wide range of other myeloid malignancies, screening is not straightforward, and the prognostic significance of TET2 mutations in ET is currently unknown.

In the presence of a pathogenetic mutation in JAK2 or MPL, a diagnosis of ET requires exclusion of PV and PMF. To this end, we find blood film examination and
assessment of iron status to be helpful. A normal hemoglobin in an iron replete patient is usually sufficient to exclude PV. Although reduced serum ferritin and/or absent bone marrow iron stores may occur in ET, we consider the combination of microcytic red cells and a normal hemoglobin in a JAK2 V617F-positive Caucasian patient highly suggestive of iron-deficient PV. In our opinion, PMF can generally be excluded by the absence of significant splenomegaly, unexplained anemia, teardrop poikilocytes and a leukoerythroblastic blood film. A minority of patients with chronic myelomonocytic leukemia harbor a JAK2 V617F mutation, although such cases generally lack thrombocytosis, with additional features such as leukocytosis, monocytosis and splenomegaly suggesting the correct diagnosis.

In patients with suspected ET who lack JAK2 and MPL mutations, exclusion of reactive causes is particularly important (Table 1). In studies of unselected patients with thrombocytosis, less than 20% harbored a clonal blood disorder. Therefore a careful history, assessment of inflammatory markers (C-reactive protein and/or erythrocyte sedimentation rate) and bone marrow histology are all recommended (Figure 1). Cytogenetic analysis may also be considered, and we use a panel of fluorescent in-situ hybridization probes to detect MPN-associated chromosome abnormalities (detecting additional copies of chromosomes 8 & 9 and deletions of 20q and 13q). However chromosomal lesions are present in only 5% of patients at diagnosis and lack prognostic significance. In the absence of a molecular or cytogenetic marker of clonal hematopoiesis, ET remains a diagnosis of exclusion.

Diagnostic criteria for ET are presented in Table 2. Criteria from the British Committee for Standards in Haematology (BCSH) are used in our clinic. These criteria are similar to those of the WHO but differ in three important respects. First, in the presence of a pathogenetic mutation a diagnosis of ET does not necessarily require bone marrow studies, as other myeloid disorders that present with
thrombocytosis and a \textit{JAK2} or \textit{MPL} mutation can generally be excluded by clinical and laboratory features as outlined above. However, it is our practice to obtain bone marrow aspirate and trephine biopsy samples from most patients at diagnosis. This is to provide both confirmatory data (bone marrow generally showing normal cellularity in the presence of giant megakaryocytes with hyperlobated nuclei) and prognostic information, specifically the degree of reticulin fibrosis\textsuperscript{11}. A bone marrow sample at diagnosis also provides a useful baseline for subsequent comparisons, for example following myelofibrotic transformation. Second, BCSH criteria do not use bone marrow histology to subdivide ET into ‘true-ET’ and ‘prefibrotic myelofibrosis’ because the existence of the latter as a distinct entity remains controversial and the underlying histological criteria are difficult to apply reproducibly\textsuperscript{14}. Third, the BCSH classification includes patients with bone marrow reticulin greater than grade 2 (on a 0-4 scale) who lack other features of PMF or myelofibrotic transformation. Under current WHO criteria, such patients cannot be classified as either ET, since they have too much reticulin, or PMF, since they have none of the clinical features required for this diagnosis.

\textit{Myelofibrotic transformation of essential thrombocytemia}

Evolution to myelofibrosis affects a proportion of ET patients, although the reported prevalence varies widely, reflecting differences in study design, therapeutic intervention and the diagnostic criteria applied. Retrospective studies suggest that myelofibrotic transformation increases with disease duration, affecting 3-10\% in the first decade after diagnosis, and 6-30\% in the second decade\textsuperscript{15-17}. Given the close relationship of post-ET myelofibrosis to PMF, the criteria we use to diagnose these conditions are essentially the same (Table 3). These criteria are similar to other widely-used systems\textsuperscript{13,18,19} but do not include serum LDH, as a correlation between increasing LDH and myelofibrotic transformation has yet to be established and a raised LDH is also found in the majority of patients with ET or PV\textsuperscript{20}. It is important to
emphasize that the development of reticulin fibrosis on its own does not equate to transformation to myelofibrosis, and diagnosis of myelofibrotic transformation is reserved for those showing bone marrow fibrosis in association with accompanying clinical and/or laboratory features (Table 3).

Leukemic transformation of essential thrombocythemia

Progression to acute myeloid leukemia (AML) occurs in a small minority of patients, with retrospective studies suggesting an incidence of 1-2.5% in the first decade after diagnosis, 5-8% in the second decade and continuing to rise thereafter\textsuperscript{15, 16, 21}. However studies often included patients who had received multiple lines of cytoreductive therapy, including alkylating agents which are known to increase the rate of leukemic transformation\textsuperscript{22, 23}, thus rendering these findings difficult to interpret. Transformation to AML is diagnosed in the presence of $\geq 20\%$ blast cells in the blood and/or bone marrow. Of note, patients with \textit{JAK2} V617F-positive ET may develop AML that is negative for the \textit{JAK2} mutation\textsuperscript{24-26}.

Controversies in the diagnosis of essential thrombocythemia

\textit{Distinguishing essential thrombocythemia from primary myelofibrosis.}

ET is heterogeneous with regards to diagnostic, clinical and laboratory features and there has been considerable debate over the existence of distinct subgroups. Some of this heterogeneity, such as variation in diagnostic blood counts and bone marrow cellularity, reflects the presence or absence of mutations in \textit{JAK2} or \textit{MPL}\textsuperscript{4, 7, 14, 27} and constitutional genetic differences are also likely to contribute. The current WHO classification proposes that bone marrow histology can be used as a tool to subdivide ET into ‘true ET’ and ‘pre-fibrotic myelofibrosis’\textsuperscript{13}, and suggests that ‘true ET’ is a benign and stable condition whereas ‘pre-fibrotic myelofibrosis’ progresses to clinically overt myelofibrosis\textsuperscript{28}. However many of the histological criteria used to define ‘pre-fibrotic myelofibrosis’, such as megakaryocyte morphology, are subjective.
and difficult to apply reproducibly, even by experienced hematopathologists. We therefore avoid the terms ‘true ET’ and ‘pre-fibrotic myelofibrosis’ in our practice.

A second area of debate relates to patients with an isolated thrombocytosis who show an increase in bone marrow reticulin fibrosis at diagnosis, but lack any other features of PMF (Figure 2). Such patients clearly have an MPN, but cannot be classified as having either ET or PMF according to WHO criteria. Importantly such cases are not unusual, with data from the PT-1 trial indicating that 15-20% of ET patients harbor grade 3 or occasionally grade 4 reticulin fibrosis at diagnosis (on a 0-4 scale, with grade 4 indicating the presence of collagen fibrosis), in the absence of other features of PMF. Increased bone marrow fibrosis at diagnosis is associated with higher rates of myelofibrotic transformation, thrombosis and hemorrhage, but no change in overall survival. The lack of a survival difference, together with the small number of complications even at higher reticulin levels, supports the concept that patients presenting with an isolated thrombocytosis but elevated reticulin have a relatively benign prognosis. We therefore follow BCSH guidelines according to which such patients are diagnosed and treated as ET.

A third area of controversy relates to the traditional view of ET and PMF as separate entities. More recently it has been suggested that PMF represents presentation in accelerated phase of a previously undiagnosed MPN, usually ET. This concept is supported by several lines of evidence: (i) PMF is clinically indistinguishable from myelofibrotic transformation of ET; (ii) the prevalence of JAK2 and MPL mutations are similar in ET and PMF; (iii) laboratory (eg. cytogenetic changes) and clinical features (eg. increased rate of leukemic transformation) suggest PMF represents accelerated phase disease; and (iv) patients with PMF may have thrombocytosis for many years prior to diagnosis (Figure 3). Of interest, the patient illustrated in Figure 3 had a platelet count of 450-500 x10^9/L at diagnosis of PMF, but was subsequently
found to have had counts close to 1,000 x10^9/L over the preceding 10 years. This indicates that ET patients presenting with marginally elevated platelet counts may represent either early phase disease (platelet count on the way up) or late phase disease (platelet count on the way down).

These various controversies over the boundary between ET and PMF are likely to be resolved in time as we gain more molecular insights into these disorders. However the current lack of a universally agreed classification will impair comparisons between clinical studies. In our view the WHO criteria place too much reliance on subjective histological criteria, the variable application of which by different centers will result in a lack of comparability between patient cohorts. By contrast the broader definition of ET adopted by BCSH guidelines has the advantage that it is easier to apply in a reproducible manner.

**Distinguishing ET from PV**

The distinction between ET and PV is, in theory, simple – patients with PV have an overt erythrocytosis that is lacking in ET. Unfortunately in practice matters are more complex. Mounting evidence demonstrates that patients with JAK2 V617F-positive ET represent a *forme fruste* of PV and exhibit PV-like features. ET and PV therefore form a phenotypic spectrum and there has been considerable debate over where to draw the line between them. Indeed there are inherent problems in using continuous variables, such as hemoglobin, hematocrit or red cell mass, to make this binary distinction, since the group of patients with borderline values will inevitably include both disorders, as illustrated in Figure 4A.

We take a pragmatic approach and base a diagnosis of PV on the presence of a *JAK2* mutation and a raised hematocrit (+/- supporting features such a low serum erythropoietin), an approach consistent with both WHO and BCSH guidelines.
We recognize that, unless markedly elevated, hematocrit does not accurately predict a raised red cell mass\textsuperscript{32}, that serum erythropoietin levels do not distinguish PV from ET\textsuperscript{7} and that ET patients, predominantly those with JAK2 V617F-positive disease, may harbor an increased red cell mass despite a normal hematocrit\textsuperscript{33, 34}. However, in the presence of a normal hematocrit and normal iron stores, the clinical significance of a raised red cell mass is unclear, and so we do not measure red cell mass in our ET patients.

Further progress in distinguishing ET from PV is likely to require a better understanding of their molecular pathogenesis. It has recently been reported that the distinct phenotypes of JAK2 V617F-positive ET and PV reflect differential STAT1 activation\textsuperscript{35}, an observation which could lead to clinically useful biomarkers.

**How we treat essential thrombocythemia**

*Modification of cardiovascular risk factors*

In our practice, all patients are screened for the presence of established cardiovascular risk factors including hypertension, diabetes, smoking, hypercholesterolemia and obesity, and treated where indicated according to local guidelines. The broad efficacy of the cholesterol-lowering statin drugs in the prevention of atherosclerotic disease has raised the possibility that such agents may be useful in ET, although this has yet to be tested in a prospective study.

*Anti-platelet therapy*

A large randomized trial in PV demonstrated a reduction in thrombotic events in those taking aspirin, without a concomitant increase in the risk of hemorrhage\textsuperscript{36}. Retrospective studies have suggested a similar protective effect in ET\textsuperscript{37, 38} although one recent study suggested that low risk patients may not derive benefit from anti-platelet therapy\textsuperscript{39}. Based on current evidence, we recommend aspirin for all ET
patients unless contraindicated. Although there is little data concerning the use of newer anti-platelet agents such as clopidogrel, their proven track record in atherosclerotic disease suggests they are appropriate for ET patients unable to tolerate aspirin.

**Indications for cytoreductive therapy**

The best established risk factors for thrombotic complications in ET are age over 60 years or a history of previous thrombosis\(^{16, 40, 41}\), and patients with these risk factors probably benefit from cytoreductive therapy\(^{42}\). Risk factors for atherosclerotic disease also predict for thrombosis in ET patients\(^{41, 43, 44}\), although it is unclear if their presence necessitates cytoreductive therapy in the absence of high risk ET (age over 60 years or history of thrombosis). The degree of thrombocytosis is not a reliable indicator of thrombotic risk, although very high levels may predict for hemorrhagic complications\(^{16, 41, 45-48}\). Meta-analysis has confirmed an increased risk of venous and arterial thrombosis in \(JAK2\) V617F-positive compared to V617F-negative ET\(^{49, 50}\). Studies have also suggested that the size of the \(JAK2\)-mutant clone may be of prognostic significance in MPN patients, although data for ET patients are limited\(^{27}\).

Increased leukocyte count or increased bone marrow fibrosis at diagnosis are also independent predictors of thrombotic complications\(^{15, 29, 48}\).

We stratify ET patients on the basis of thrombotic risk (Table 4), and recommend cytoreductive therapy for all high risk patients. Cytoreduction is also considered in those with prior serious hemorrhage (eg requiring hospitalization or red cell transfusion) which is thought to be ET-related. Microvascular complications such as erythromelalgia generally settle with anti-platelet therapy alone\(^{38}\), and cytoreductive therapy is only considered for refractory cases. Those with indicators of atherosclerotic disease in the absence of high risk ET are assessed on a case by case basis, taking into account the severity of each cardiovascular risk. For example
in the absence of high-risk features, cytoreductive therapy would not generally be recommended for a patient with well-controlled hypertension, but would be considered in someone with poorly controlled diabetes or a strong family history of early-onset atherosclerotic disease. The role of the platelet count in directing cytoreductive therapy remains contentious. Many physicians still recommend cytoreductive therapy in patients with platelets > $1,500 \times 10^9$/L, although it may be reasonable to use a higher cut-off in younger patients. There are, as yet, no prospective clinical data on the utility of novel thrombotic risk factors, such as JAK2 mutation status, mutant allele burden, leukocyte count and bone marrow fibrosis. We therefore do not currently use these factors to guide therapeutic decisions.

Patients without high-risk features can be divided into low risk (age < 40 years) and intermediate risk (age 40-60 years). Cytoreductive therapy is unlikely to offer a significant protective effect for those with low risk disease, in whom the a priori risk of thrombosis is small. There is currently little evidence available to guide treatment decisions in the intermediate risk group. The on-going PT-1 trials (http://www.haem.cam.ac.uk/pages/pt1/), comprising a randomized trial of hydroxycarbamide and aspirin versus aspirin alone for intermediate risk patients and an observational study of low risk patients treated with aspirin alone, will provide prospective data to help clarify therapeutic decisions for these patients.

**Choice of cytoreductive agent**

Hydroxycarbamide (also known as hydroxyurea) is the only cytoreductive agent proven to reduce thrombotic events in a randomized controlled trial\(^{42}\), and remains our recommended first line therapy for the majority of patients requiring treatment (Table 5). Concerns have been raised, however, about a possible increased risk of leukemic transformation with this agent. Clinical studies have given conflicting results\(^{23, 51-54}\), further confounded by inclusion of patients who have received multiple
cytotoxic agents, lack of proper controls, retrospective data collection and relatively short follow-up. Further evidence cited in support of a mutagenic role for hydroxycarbamide includes a possible association with deletions of 17p (harboring the TP53 locus)\(^{51, 55-57}\), increased risk of skin neoplasia during prolonged therapy\(^{58}\) and possible clastogenic activity in vitro\(^{59}\). By contrast, hydroxycarbamide appears non-leukemogenic in the treatment of sickle cell disease\(^{60}\) and does not appear to increase in vivo mutation rates in sickle cell or MPN patients\(^{61}\). At this time it is unclear whether single agent hydroxycarbamide is leukemogenic; however any increased risk is likely to be small and should be balanced against the reduction in thrombotic complications, as thrombosis remains the major source of morbidity in ET.

Anagrelide reduces the platelet count by inhibition of megakaryocyte differentiation\(^{62}\) and we currently use it as second line therapy for patients in whom hydroxycarbamide is inadequate or not tolerated. Combined therapy with anagrelide and hydroxyurea has also been used successfully in our clinic where hydroxyurea alone has failed to control the platelet count. Anagrelide does not affect the white cell count but anemia is common and often progressive\(^{29}\). Up to a third of patients cannot tolerate anagrelide due to side effects, many of which result from its vasodilatory and positive inotropic actions including palpitations and arrhythmias, fluid retention, heart failure and headaches\(^{19, 63}\). Use of this drug requires particular caution in elderly patients or those with pre-existing cardiac disease. Although anagrelide is not cytotoxic, and therefore unlikely to be leukemogenic, the PT-1 trial demonstrated that anagrelide plus aspirin was inferior to hydroxycarbamide plus aspirin in high-risk ET patients. Despite equivalent control of the platelet count, anagrelide treated patients experienced higher rates of arterial thrombosis, major hemorrhage and progression to myelofibrosis, and were more likely to be intolerant of their therapy\(^{19}\). In contrast to hydroxycarbamide, anagrelide therapy was also associated with an increase in bone marrow reticulin over time\(^{29}\). Comparison of patients in the PT-1 (comparison of
hydroxycarbamide versus anagrelide\textsuperscript{19}) and Italian (comparison of hydroxycarbamide versus no cytoreductive therapy\textsuperscript{42}) prospective studies suggests that anagrelide provides partial protection from thrombosis\textsuperscript{64}. The reduced efficacy of anagrelide compared to hydroxycarbamide in thrombosis prevention was limited to those with \textit{JAK2} V617F-positive ET, probably reflecting increased sensitivity of these patients to the cytoreductive effects of hydroxycarbamide\textsuperscript{7}. However the increased risk of myelofibrotic transformation associated with anagrelide was observed in V617F-positive and negative patients.

Preliminary reports of the final results of the ANAHYDRET trial (comparing hydroxycarbamide to anagrelide) claim to show that anagrelide is not inferior to hydroxycarbamide in the treatment of ET\textsuperscript{65}. However, compared to PT-1, the number of patients enrolled was small, the duration of follow-up relatively short (539 patient-years compared to 2,653 patient-years in PT-1) and considerably fewer end-point events were recorded\textsuperscript{30}. It therefore seems highly unlikely that the ANAHYDRET study had the statistical power necessary to detect the differences observed in the PT-1 study. In addition, the ‘non-inferiority’ design of the ANAHYDRET study seems inappropriate, especially after the marked inferiority documented by the PT-1 trial. Such designs define non-inferiority up to a pre-determined limit of ‘tolerable inferiority’, but often this limit is entirely arbitrary or selected with an eye on obtaining regulatory approval, and risks failing to detect clinically relevant differences between the treatment arms. Indeed the whole ethical basis for conducting non-inferiority trials has recently been called into question\textsuperscript{66}.

Recombinant interferon alpha is free from leukemogenic or teratogenic effects, is effective at controlling the platelet count in ET and may reduce \textit{JAK2} mutant allele burden\textsuperscript{67, 66}. It should be noted, however, that interferon has not been shown to protect from thrombotic complications, and the PT-1 trial reminds us that two agents
which result in equivalent control of the platelet count may none-the-less be associated with very different thrombotic risk\textsuperscript{19}. Interferon therapy is still considered by many as experimental, and its use in the MPN is not licensed in Europe or North America. Therapy is often associated with significant side-effects, and although pegylated interferon may be more convenient, toxicity appears similar to the native compound\textsuperscript{67, 69}. Interferon is used in our clinic for young patients (typically those aged <40 years), for those wishing to start a family, or for those in whom hydroxycarbamide may be inappropriate. We try and avoid interferon in older patients who are generally less able to tolerate this agent.

Radioactive phosphorus and alkylating agents such as busulphan are effective at controlling the platelet count, but are associated with an increased risk of progression to acute leukemia, particularly when used sequentially with hydroxycarbamide\textsuperscript{23, 52}. Both agents can be given intermittently with long intervals between doses, and may be useful in treating older patients who are unable to attend the clinic on a regular basis. Pipobroman, a piperazine derivative, is effective at reducing the platelet count in ET, although there is little direct evidence for thrombosis prevention\textsuperscript{70}. Pipobroman is chemically similar to the alkylating agents and is associated with an increased risk of leukemic transformation when used in the long-term treatment of PV\textsuperscript{71}. In our clinic, the use of pipobroman and other alkylating agents is restricted to older patients (typically those aged >75 years), where they are used as second or third line agents for those who are unable to tolerate hydroxycarbamide, for example due to non-healing leg ulcers.

\textit{Response to therapy}

The traditional goal of cytoreductive therapy in ET has been resolution of symptoms and normalization of the platelet count. However retrospective studies have identified an association between leukocytosis and thrombosis\textsuperscript{48}, raising the possibility that
controlling the white cell count may be important. Recent prospective data from the PT-1 trial have shed further light on this issue, with analysis of blood counts revealing that a leukocyte (but not platelet) count above the normal range during follow-up predicted for thrombosis in the subsequent 60 days (Campbell PJ et al, in preparation). We now use freedom from ET-related symptoms together with normal platelet and leukocyte counts as our primary therapeutic endpoints, although it should be noted that this approach has yet to be validated in a prospective clinical study.

Special considerations: pregnancy

First trimester fetal loss complicates 25-50% of pregnancies in ET patients, with other complications such as intrauterine growth retardation, stillbirth and pre-eclampsia also occurring more frequently72-77. Such complications occur irrespective of the platelet count prior to conception but appear to be more common in those with JAK2 V617F-positive disease74, 77. Whether the use of aspirin or cytoreductive agents can improve pregnancy outcome is uncertain, with studies reporting contradictory results72-77. Moreover aspirin during pregnancy does not benefit non-ET patients with a history of recurrent miscarriage78. However a large meta-analysis of non-ET pre-eclampsia patients suggested that aspirin use in pregnancy is safe for mother and fetus79, and we therefore recommend aspirin for all pregnant ET patients (unless otherwise contraindicated).

We consider the use of cytoreductive therapy for all pregnant women with a history of thrombosis. We also consider cytoreductive therapy for those with previous obstetric complications, such as stillbirth or recurrent miscarriage. Since the platelet count often falls during pregnancy, we do not consider a platelet count of greater than 1,500 x10⁹/L as an absolute indication for cytoreductive therapy, and such patients are considered on a case by case basis.
Although hydroxycarbamide has been used during pregnancy, usually without adverse effects for mother or fetus, it is teratogenic in non-human mammals\textsuperscript{80} and should therefore be avoided. Anagrelide can cross the placenta with unknown effects on fetal development and should also be avoided. Interferon alpha is non-teratogenic and is the agent of choice should cytoreductive therapy be required. Although studies in ET are lacking, thromboprophylaxis appears safe in pregnancy\textsuperscript{81}, and may be considered for patients with a history of thrombosis or recurrent pregnancy loss; in those with prior thrombosis, treatment should be continued for at least 6 weeks post-partum. Overall, pregnancy does not appear to affect the natural history of ET\textsuperscript{72}.

Pregnant ET patients should ideally be managed in a center where regular fetal monitoring can be performed, with good communication between the obstetric, hematology and anesthetic departments. In animal studies, hydroxycarbamide is associated with reduced spermatogenesis and genetic damage to spermatogonia\textsuperscript{80}. We therefore advise male patients requiring cytoreductive treatment to switch to interferon alpha prior to attempted conception.

**Special considerations: surgery**

Although peri-operative thrombotic and bleeding complications appear increased in ET patients, it is not clear whether this can be ameliorated by therapeutic intervention\textsuperscript{82}. In general, we stop anti-platelet agents 7-10 days prior to major surgery or surgery to critical sites, and reintroduce as soon as the surgeon is confident of hemostasis. Post-operative thromboprophylaxis is recommended according to usual guidelines for the specific procedure. For patients on cytoreductive therapy undergoing elective surgery, the blood count is optimized pre-operatively and interruptions in therapy are kept to a minimum. For patients not receiving cytoreductive treatment, temporary therapy is considered on a case by case basis, following assessment of the individual’s thrombotic risk profile, degree of
thrombocytosis (as higher platelet counts may predict for hemorrhage\textsuperscript{47}) and the nature of the surgery. Splenectomy in ET patients generally results in a sharp increase in platelet count that may lead to thrombotic and hemorrhagic complications. Unless otherwise contraindicated, we commence cytoreductive therapy prior to splenectomy in ET patients with an increased or high-normal platelet count, aiming for a platelet count in the mid-normal range prior to surgery. Post-operative thromboprophylaxis and daily monitoring of bloods counts are also recommended.

\textit{How we treat advanced-phase disease}

The problems and complications associated with myelofibrotic transformation of ET are similar to de novo PMF, and we manage the conditions in the same way. Therapy of post-ET AML is often limited by the age and co-morbidities and supportive treatment is often the most appropriate strategy. Overall the prognosis of AML secondary to an MPN is very poor. Younger patients who achieve remission with AML induction therapy are considered for allogeneic bone marrow transplantation.

\textit{Controversies in the management of essential thrombocytemia}

\textit{The choice of cytoreductive therapy in the younger patient}

Hydroxycarbamide has proven efficacy in the prevention of thrombosis, the major source of morbidity in this condition, but concerns remain about potential leukemogenicity\textsuperscript{57}. As the incidence of leukemic transformation in ET increases with disease duration\textsuperscript{15, 16}, this concern is particularly relevant to younger patients who may require therapy for several decades. Interferon alpha is not leukemogenic, but efficacy data are lacking and some patients experience intolerable side-effects. Anagrelide is not cytotoxic and likely not mutagenic. However the PT-1 trial demonstrated inferiority of anagrelide to hydroxycarbamide in the prevention of
thrombosis, and identified an increased risk of myelofibrotic transformation with anagrelide therapy. It is our current practice to recommend a trial of interferon alpha to patients under the age of 40 years who require therapy. Approaches to maximizing tolerance include slow escalation from a low starting dose (e.g., 1MU three times a week initially), administration at bedtime with prophylactic acetaminophen (paracetamol), dose reduction once control is achieved (to the lowest dose which affords blood count control), and support from specialist nursing staff between visits to the clinic. If interferon alpha is not tolerated, the pros and cons of hydroxycarbamide versus anagrelide are discussed in detail with the individual patient. For those receiving anagrelide, we recommend baseline bone marrow studies to assess reticulin fibrosis with follow-up bone marrow histology every 2-3 years whilst therapy continues. Cessation of anagrelide should be considered in those with increasing reticulin fibrosis, as anagrelide-associated fibrosis is reversible in some cases.

Indications for cytoreductive therapy in essential thrombocythemia versus polycythemia vera

As outlined above, ET and PV form a phenotypic continuum with significant overlap in hemoglobin and platelet levels. These observations call into question the rationale for different therapeutic strategies in these two disorders, particularly the use of a target hematocrit level to guide treatment in PV but not ET. The primary aim of therapeutic intervention in both ET and PV is the prevention of thrombosis. Whereas thrombotic risk appears higher in V617F-positive compared to V617F-negative ET, retrospective data suggest comparable thrombosis rates in V617F-positive ET and PV. Common predictors of thrombosis in ET and PV include older age, thrombotic history and increased white cell count, with hematocrit identified by some but not all studies as an important predictor of thrombosis in PV. Given the
similarities between V617F-positive ET and PV, the time may be approaching when these disorders are stratified and managed as a single disease entity, with older age, history of prior thrombosis or a raised hematocrit indicating high risk disease and mandating cytoreductive therapy. Given the lower thrombosis rates in V617F-negative ET, it may be that indications for therapy could safely be relaxed in this group. Clearly further prospective trials are necessary before these goals can be realized, with studies enrolling both ET and PV patients allowing for prospective comparison of complication rates and assessment of novel risk factors such as mutation status, leukocyte count and bone marrow fibrosis.

**Future directions**

The last five years have witnessed dramatic advances in our understanding of the pathogenesis, classification and therapy of ET. The identification of additional molecular markers is likely to be needed to clarify the overlap between ET, PV and PMF. Novel risk factors such as leukocyte count, JAK2 mutation status and bone marrow fibrosis may provide more precise therapeutic stratification, an approach that awaits validation in prospective studies. With regards to therapy, direct comparison of interferon alpha and hydroxycarbamide seems timely. JAK2 inhibitors may prove useful for accelerated phase disease but given the excellent prognosis of chronic phase ET, it is unclear whether there is likely to be a role for JAK2 inhibitors in the majority of ET patients.
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Author contribution

PAB, WNE, PJC and ARG all contributed to the manuscript.
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<td>Drug effect (vincristine, epinephrine, all-trans-retinoic acid)</td>
</tr>
<tr>
<td>Hyposplenism or congenital absence of spleen</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td><strong>Familial thrombocytosis</strong></td>
</tr>
<tr>
<td>Mutations in TPO, MPL or unknown genes</td>
</tr>
<tr>
<td><strong>Spurious thrombocytosis</strong></td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Cytoplasmic fragmentation accompanying myeloid or lymphoid neoplasia</td>
</tr>
<tr>
<td>Red cell fragmentation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>A1</td>
</tr>
<tr>
<td>A2</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>A3</td>
</tr>
<tr>
<td>A4</td>
</tr>
</tbody>
</table>

†Increased reticulin fibrosis excludes a diagnosis of ET
Table 3. Criteria for the diagnosis of myelofibrosis

<table>
<thead>
<tr>
<th>Primary myelofibrosis</th>
<th>Myelofibrotic transformation of ET or PV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Requires A1+A2 and any two B criteria</strong></td>
<td><strong>Requires A1+A2 and any two B criteria</strong></td>
</tr>
<tr>
<td>A1</td>
<td>Bone marrow fibrosis ≥3 (on 0–4 scale)</td>
</tr>
<tr>
<td>A2</td>
<td>Pathogenetic mutation (eg in JAK2 or MPL) or absence of both BCR-ABL1 and reactive causes of bone marrow fibrosis</td>
</tr>
<tr>
<td>B1</td>
<td>Palpable splenomegaly</td>
</tr>
<tr>
<td>B2</td>
<td>Unexplained anemia</td>
</tr>
<tr>
<td>B3</td>
<td>Leukerythroblastic blood film</td>
</tr>
<tr>
<td>B4</td>
<td>Tear-drop red cells</td>
</tr>
<tr>
<td>B5</td>
<td>Constitutional symptoms†</td>
</tr>
<tr>
<td>B6</td>
<td>Histological evidence of extramedullary hematopoiesis</td>
</tr>
</tbody>
</table>

†Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37.5°C) or diffuse bone pains

Criteria adapted from Campbell and Green 2006

Table 4. Risk stratification for patients with essential thrombocythemia

<table>
<thead>
<tr>
<th>High risk</th>
<th>No high risk features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Age &lt;40 years</td>
</tr>
<tr>
<td>Prior thrombosis</td>
<td>Age 40-60 years</td>
</tr>
<tr>
<td>Platelets &gt;1,500 x10⁹/L</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Choice of cytoreductive agent in essential thrombocytemia

<table>
<thead>
<tr>
<th>Age group</th>
<th>First line</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years old</td>
<td>Interferon</td>
<td>Hydroxycarbamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anagrelide</td>
</tr>
<tr>
<td>40-75 years</td>
<td>Hydroxycarbamide</td>
<td>Interferon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anagrelide</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>Hydroxycarbamide</td>
<td>Anagrelide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pipobroman</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Busulphan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radioactive phosphorus</td>
</tr>
</tbody>
</table>
Figure legends

**Figure 1. Algorithm for the investigation and diagnosis of thrombocytosis.**
ET, essential thrombocythemia; PV, polycythemia vera; PMF, primary myelofibrosis; MCV, mean cell volume; FBC, full blood count; MPN, myeloproliferative neoplasm.

**Figure 2. Isolated thrombocytosis and bone marrow fibrosis in the absence of clinical features to support a diagnosis of primary myelofibrosis.** (A) Bone marrow samples obtained at diagnosis from a 54 year old female with thrombocytosis in the absence of additional features of PMF; bone marrow aspirate stained with Wright-Giemsa showing a large megakaryocyte with a hyperlobated nucleus; bone marrow trephine biopsy stained with hematoxylin and eosin showing loose clusters of megakaryocytes containing both large megakaryocytes with hyperlobated nuclei and smaller forms with cloud-like or hyperchromatic nuclei; silver-stained bone marrow section showing grade 4 reticulin fibrosis (on 0-4 scale). (B) Blood counts over 54 months from diagnosis showing stabilization of the platelet count and no change in hemoglobin level. Red and blue shaded areas represent the normal range for hemoglobin and platelet count respectively.

**Figure 3. Presentation with myelofibrotic transformation of previously undiagnosed essential thrombocythemia.** (A) Platelet and hemoglobin levels over a 10 year period prior to presentation with PMF at the age of 67 years; a marked thrombocytosis between 8 and 10 years prior to diagnosis is followed by a gradual fall in platelet count and progressive anemia in the absence of iron deficiency or inflammation. (B) At clinical presentation, Wright-Geimsa stained blood film showing leukoerythroblastosis and tear-drop red cells; hematoxylin and eosin stained bone marrow trephine biopsy showing clusters of dysplastic megakaryocytes; silver-stained bone marrow trephine biopsy showing grade 4 reticulin fibrosis (on 0-4...
scale). Red and blue shaded areas represent the normal range for hemoglobin and platelet count respectively.

**Figure 4. Distribution of hematocrit level in JAK2 V617F-positive disease.** (A) Diagrammatic representation of hemoglobin levels in patients with JAK2 V617F-negative ET, V617F-positive ET and V617F-positive PV, showing mean hemoglobin levels for patients with V617F-positive and negative ET (from reference 7) and V617F-positive PV (from Cambridge cohort); hemoglobin levels in the mid-range will include patients with both ET and PV. (B) Hematocrit levels at diagnosis from a cohort of patients attending the Cambridge MPN clinic and diagnosed with JAK2 V617F-positive ET or PV, showing considerable overlap in hematocrit between ET and PV in both male and female patients.
**Clinical case:**

- 54 year old female presenting with isolated thrombocytosis in the absence of anemia (Hb 13.6 g/dL) without leukocytosis, leukaerythroblastosis, clinical splenomegaly or raised inflammatory markers. Serum LDH was elevated at 470 (normal range 120-240); however a raised LDH is found in the majority of patients with ET, PV and PMF\(^\text{18}\).
- Negative for mutations in JAK2 and MPL.
- Bone marrow aspirate showing hyperlobated megakaryocytes
- Bone marrow trephine biopsy showing increased cellularity with megakaryocyte atypia and grade 4 reticulin fibrosis (on a 0-4 scale).
- Treated with aspirin alone; stable disease over subsequent 54 months.

---

**Figure 2**

A

B

---

**Hemoglobin**

**Platelets**

![Graph](http://example.com/graph.png)

---

\(^\text{18}\) Ruckert J, et al. \(\text{Blood} \text{2017} \text{130} \text{1795-1800}\).
Clinical case:
• 67 year old female presenting with anemia, splenomegaly, leukoerythroblastic blood film, dysplastic megakaryocyte morphology and grade 4 bone marrow fibrosis: diagnosed with PMF (JAK2 and MPL mutation negative).
• Persistent thrombocytosis noted over ten years prior to presentation; iron studies and inflammatory markers repeatedly normal.
• Presentation with PMF preceded by a gradual fall in platelet and hemoglobin levels.
• Findings suggest previously undiagnosed ET with myelofibrotic transformation at presentation.
Figure 4

A

<table>
<thead>
<tr>
<th>JAK2 wild-type</th>
<th>JAK2 V617F</th>
<th>V617F-homozygous?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of cases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hemoglobin (g/dL): 13.5 14.5 17.8

ET  ET or PV  PV

B

Patients diagnosed with JAK2 V617F-positive ET or PV

Number of patients

Diagnostic hematocrit
How we treat essential thrombocythemia

Philip A Beer, Wendy N Erber, Peter J Campbell and Anthony R Green