Management of Polycythemia Vera and Essential Thrombocythemia

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The optimal management of patients with polycythemia vera (PV) and essential thrombocythemia (ET) continues to be controversial. Both diseases present diagnostic challenges and there is a paucity of data from randomized clinical trials to guide therapeutic decisions. However, the past two years have seen major advances in our understanding of these myeloproliferative disorders (MPD). First, the ECLAP study demonstrated the anti-thrombotic efficacy of aspirin in patients with PV.[1] Second, the PT-1 trial, the largest randomized study of any MPD, has provided much needed guidance on the optimal management of patients with ET.[2] Third, the identification of a single JAK2 mutation in most patients with PV, and in some of those with ET, illuminates the pathogenesis of these diseases and raises questions about the boundary between them.[3-7] For the purpose of management decisions, it remains appropriate to consider them as separate entities for the time being. However, as we learn more about the clinical significance of the JAK2 mutation, it seems likely that the coming years will see major changes in the way we classify and manage these disorders.

Polycythemia Vera

Diagnosis

The Polycythemia Vera Study Group (PVSG) first developed a set of rigorous criteria for the diagnosis of polycythemia vera (PV) in the 1970s. A number of the original criteria have been superceded by the development of newer tests.[8] Proposed diagnostic criteria for the diagnosis of PV incorporating the JAK2 V617F mutation are presented in **Table 1**. The JAK2 mutation is present in most patients with PV, but it is also present in half of those with ET or idiopathic myelofibrosis (IMF). Establishing the presence of an absolute erythrocytosis (usually by demonstrating a raised red cell mass) therefore remains important for distinguishing PV from other MPDs positive for the JAK2 mutation. It is likely that, with the establishment of PCR-based methods for detecting the JAK2 V617F mutation, this tool will become routinely available in laboratories offering molecular diagnostic services. This will allow most patients to be diagnosed on the basis of a raised red cell mass, normal O_2 saturation (or absence of a raised serum erythropoietin) and positive allele-specific PCR for JAK2 V617F. It is also important to emphasize that the V617F mutation has been identified in a small proportion of other hematological malignancies (for example, acute myeloid leukemia, chronic myelomonocytic leukemia and myelodysplasia).

However, none of these disorders is associated with a raised red cell mass and clinical distinction from PV is rarely an issue.

The reported prevalence of PV patients lacking the JAK2 mutation has varied from 70% to nearly 100%. The lower end of this range is likely to reflect the use of relatively insensitive diagnostic methods and/or less rigorous diagnostic criteria. When investigating V617F-negative patients who appear to have PV, it is therefore particularly

Table 1. Proposed diagnostic criteria for polycythemia vera (PV).

A1.　Raised red cell mass (> 25% above predicted, or hematocrit ≥ 0.60 in males or > 0.56 in females)[a]

A2.　Absence of causes of secondary erythrocytosis (normal arterial oxygen saturation and no elevation of serum erythropoietin.)[b]

A3.　Palpable splenomegaly

A4.　Presence of JAK2 V617F mutation or other cytogenetic abnormality (excluding *BCR-ABL*) in hemopoietic cells

B1.　Thrombocytosis (platelets > 400 x 10^9/L)

B2.　Neutrophilia (neutrophils > 10 x 10^9/L; > 12.5 x 10^9/L in smokers)

B3.　Radiological splenomegaly

B4.　Endogenous erythroid colonies or low serum erythropoietin

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A1 + A2 + either another A or two B criteria is required for a diagnosis of PV

[a] These hematocrit values are invariably associated with a raised red cell mass in an adult population.

[b] Note that it is possible in rare cases for PV to coexist with a cause of secondary erythrocytosis.

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important to exclude secondary causes of erythrocytosis by looking for a suggestive clinical history, reduced arterial O_2 saturation, raised serum erythropoietin levels or renal abnormalities on ultrasound. However, the existence of even a small number of V617F-negative PV patients justifies the continued use of the B criteria (**Table 1**) for the time being. Although marrow histology has been included as a minor criterion in the WHO classification,[9] the role of bone marrow biopsy in the evaluation of PV remains controversial because of inter-observer variation in quantifying erythroid and megakaryocytic proliferation.

It has recently been demonstrated that V617F-positive patients with essential thrombocythemia (ET) exhibit many similarities with PV (see below).[7] These results suggest that the two disorders may be better viewed as a continuum with the degree of erythrocytosis determined by physiological or genetic modifiers (**Figure 1A**; see Color Figures, page 552). This model suggests that, in patients at the thrombocythemia end of the continuum, the effects of the V617F mutation on erythropoiesis are constrained by physiological mechanisms, including erythropoietin suppression and depleted iron stores, or by genetic modifiers, either acquired or constitutional. Acquisition of homozygosity for the V617F mutation may favor development of a polycythemic phenotype since homozygosity for mutant *JAK2* occurs in approximately 30% of patients with PV, but is rare in ET. [3-6] Gender may influence presentation of V617F-positive disease, since PV is more common in men,[10,11] whereas V617F-positive thrombocythemia is more common in women. Other genetic modifiers are likely to influence disease phenotype in a manner analogous to polygenic predisposition to many common diseases, a concept which may also account for the variability in platelet count, white cell count and marrow fibrosis in V617F-positive patients.

Over the past few years several potentially useful markers have been described,[12-14] including increased expression of *PRV1* and BCL-X$_L$, and diminished platelet MPL expression, but none are available outside specialized centers and all are likely to become redundant with the advent of testing for the JAK2 mutation.

Clinical course

The prognosis of untreated PV in the first half of the 20th century was dismal with a median survival of approximately 18 months. However, the advent of venesection, together with antithrombotic and cytoreductive agents, has greatly improved the outlook. Patients with PV have an increased mortality compared with the general population.[10] Thrombosis is particularly prevalent in older patients, whereas transformation to acute leukemia or myelofibrosis may account for reduced survival of younger patients. The clinical epidemiology of PV has been reviewed recently.[11,15] Two large Italian studies (GISP and ECLAP) have provided important insights into the natural history of PV. In both studies, overall mortality was approximately 3 per 100 pa-

tients/year. Compared to age- and sex-matched controls, the risk of death from cardiovascular causes was modestly increased (1.4-fold), whereas the risk of death from hematological transformation was markedly increased (36.1-fold),[11] and major thrombosis also occurred in approximately 3 per 100 patients/year. Age over 65 years and history of a prior thrombosis were the most important risk factors identified for the development of additional thrombotic events. Duration of disease and age > 70 years were associated with an increased risk of developing myelofibrosis and leukemia, respectively.

Clinical trials

Over the past 25 years, several clinical trials have investigated the optimal management of PV, and these have been reviewed recently.[15] In the 1970s, the PVSG-01 study randomized 431 patients to venesection alone, phosphorus 32 (^{32}P) plus venesection or chlorambucil plus venesection. Patients treated with venesection alone had a better median survival (13.9 years) than those in the other two arms (11.8 and 8.9 years, respectively). However, patients in the venesection arm showed an excess mortality within the first 2-4 years mainly caused by thrombotic events, whereas patients in the other two arms subsequently showed a higher rate of leukemia and other malignancies. The PVSG-05 and 08 trials were designed to try to reduce the major causes of death identified in the PVSG-01 trial. In an attempt to lower the thrombotic events seen in the venesection-only arm, the PVSG-05 study reduced the target hematocrit to 0.45 and compared venesection plus aspirin (900 mg/day) and dipyridamole (225 mg/day) with venesection plus ^{32}P. The study was terminated early (median follow-up 1.2 years) because patients in the venesection/aspirin/dipyridamole arm exhibited a high incidence of major gastrointestinal hemorrhage (presumably reflecting the high doses of aspirin and dipyridamole) and no reduction in thrombotic events. The PVSG-08 study compared 51 patients receiving hydroxyurea for a median period of 8.6 years with historical controls from the venesection-only arm of PVSG-01. Although no significant differences were observed, the hydroxyurea group tended to suffer fewer total deaths (39% vs 55%), less myelofibrosis (8% vs 13%), and more acute leukemia (10% vs 4%). However, the analysis excluded any patient in the venesection-only arm whose disease required cytoreductive therapy, and so this arm was highly selected and likely to represent a good-prognosis subgroup.

In Europe, the EORTC compared 293 patients randomized to busulfan or ^{32}P and followed for a median of 8 years. Survival at 10 years was significantly better in the busulfan arm mainly because of a lower incidence of vascular deaths. Najean and colleagues compared 292 patients below the age of 65 years randomized to pipobroman or hydroxyurea with a follow-up of 16 years. No significant difference was observed in the incidence of death, thrombosis or acute leukemia. However, patients treated with hydroxy-

urea exhibited a high rate of developing myelofibrosis, possibly related to the fact that platelet counts were significantly less well controlled. The French group also compared 461 patients over 65 years of age randomized to ^{32}P alone or in combination with hydroxyurea and who were followed for up to 16 years. No difference in overall survival was observed, but an increase in hematological and other malignancies was noted in patients receiving both ^{32}P and hydroxyurea.

The most recent randomized study (ECLAP) compared 518 patients randomized to receive aspirin (100 mg/day) or no aspirin.[1] There was no difference in overall mortality, cardiovascular mortality or major bleeding. However, treatment with aspirin significantly reduced the risk of the combined end point of nonfatal myocardial infarction, nonfatal stroke, major venous thrombosis and death from cardiovascular causes. These results suggest that low-dose aspirin can reduce thrombotic complications in patients with PV.

Although there are no randomized data, interferon and anagrelide may have a role in subgroups of patients with PV. Interferon is often favored in young patients, since it is not thought to be leukemogenic or teratogenic, and remains the treatment of choice when cytoreduction is required during pregnancy. Its main drawbacks are that it is expensive, requires parenteral administration and produces considerable side effects. However, the development of pegylated interferon allows once-weekly dosage. Anagrelide specifically reduces the platelet count (and the hemoglobin in some patients) without affecting the white cell count. Its efficacy and side effects are discussed below, but there is no suggestion that it is leukemogenic.

Recommendations for management

Based on the limited evidence described above, current recommendations for management are outlined in **Table 2**. Venesection remains the central feature of initial treatment with a target hematocrit of 0.45 based on the seminal studies by Pearson and Wetherley-Mein.[16] The ECLAP study,[1] together with primary and secondary prevention studies in patients without PV,[17,18] argue strongly for the use of low-dose aspirin in all patients lacking a clear contraindication. It also seems sensible for other predictors of cardiovascular morbidity (hypertension, diabetes mellitus, smoking, hypercholesterolemia, congestive heart failure) to be managed aggressively.[15]

Cytoreductive therapy is clearly indicated if patients are intolerant of venesection or if they develop symptomatic splenomegaly thought to be due to disease progression. The treatment of thrombocytosis is more controversial. It has been suggested that it is unnecessary to control the platelet count in patients with PV, particularly since a clear relationship between platelet number and thrombosis has not been established.[19] However, several lines of evidence suggest that controlling the platelet count is likely to be beneficial for patients with PV:

(1) The ECLAP study[1] strongly suggests that platelets

contribute to thrombosis in patients with PV.
(2) The beneficial effect of controlling the platelet count has been demonstrated by Barbui and co-workers[20] in the closely related disorder ET.
(3) Treatment with cytoreductive agents reduced thrombotic events in patients with PV in the PVSG-01, -05 and -08 studies. The incidence of thromboses in the venesection only arm of PVSG-01 was 32.8% after 7.5 years, whereas among patients treated with hydroxyurea in PVSG-08 the incidence was 9.8% at the same time point. Although the target hematocrit in the early stages of the PVSG-01 trial would now be viewed as too high, in a separate study in which hematocrits and platelets were more tightly controlled at < 0.45 and $< 400 \times 10^9$/L, respectively, the thrombosis rate was reduced to 5.6% after 7-8 years.[21]
(4) Two French trials[22,23] have produced data consistent with the idea that a persistently raised platelet count is associated with an increased risk of developing myelofibrosis. It has been suggested that the development of myelofibrosis does not have adverse prognostic implications, but the difficulty with this assertion is the variable definition of myelofibrosis. Some patients with increased reticulin as an isolated finding can have prolonged survival, but it seems probable that the development of clinically overt myelofibrosis in a patient with PV is associated with a poor prognosis.

No one of these arguments is definitive on its own, but the current balance of evidence suggests that it is sensible to control the platelet count in most patients with PV, although in young patients (< 40 years) with a low risk of thrombosis, it may be reasonable to use aspirin alone. In most patients, hydroxyurea represents the first-line cytoreductive agent. Although doubts remain about possible long-term

Table 2. Recommendations for management of patients with polycythemia vera (PV).

1. Venesection to maintain hematocrit < 0.45

2. Low-dose aspirin (unless contraindicated)[a]

3. Manage reversible thrombotic risk factors aggressively (e.g., smoking, hypertension, hypercholesterolemia, obesity)

4. Consider cytoreduction if
   (i) patient intolerant of venesection
   (ii) thrombocytosis develops
   (iii) symptomatic or progressive splenomegaly

5. Choice of cytoreductive therapy:
   (i) < 40 years – interferon-α[b]
   (ii) > 40 years – hydroxyurea[b,c]

[a]Avoid aspirin while platelet count $> 1500 \times 10^9$/L.
[b]Anagrelide plus venesection may be useful in patients intolerant of or resistant to hydroxyurea and interferon.
[c]Consider ^{32}P or intermittent use of busulfan if patient is very elderly and outpatient attendance is impractical.

leukemogenicity, there are no robust data which show that, when used as a single agent, it increases the risk of leukemia (see below). Interferon-α is useful in young patients and during pregnancy. Anagrelide may be useful for control of the platelet count when hydroxyurea and interferon-a are unsuitable. In very elderly patients for whom regular clinic attendance is impractical, ^{32}P or intermittent busulfan may still have a place.

Essential Thrombocythemia

Classification

Analysis of 776 patients with ET demonstrated that just over half had the JAK2 V617F mutation, and this divided patients into two biologically distinct subgroups.[7] V617F-positive patients displayed multiple features resembling PV, with significantly higher hemoglobin levels, neutrophil counts, bone marrow erythropoiesis and granulopoiesis, more venous thromboses and a higher incidence of polycythemic transformation. In addition, mutation-positive patients had lower serum erythropoietin and ferritin levels than V617F-negative patients with ET. These results imply that V617F-positive thrombocythemia and polycythemia may be better viewed as a continuum, and not as two distinct entities (**Figure 1A**; see Color Figures, page 552). V617F-negative individuals with ET do nonetheless exhibit features characteristic of an MPD, including cytogenetic abnormalities, hypercellular bone marrow with abnormal megakaryocyte morphology, *PRV1* overexpression, growth of erythropoietin-independent erythroid colonies, and a risk of myelofibrotic or leukemic transformation.[7] These facts suggest that ET should be subclassified as either V617F-positive or V617F-negative ET, both *bona fide* MPDs, although future studies may prove V617F-negative ET to be biologically heterogeneous.

These data are consistent with two models for the relationship between V617F-negative and V617F-positive thrombocythemia. The first model postulates that the JAK2 V617F mutation is neither necessary nor sufficient for the development of an MPD phenotype, but occurs in a subclone with a preceding unknown mutation[6] (**Figure 1B**; see Color Figures, page 552). Under such a model, the first, unknown mutation gives rise to V617F-negative thrombocythemia, which subsequently evolves into V617F-positive thrombocythemia with acquisition of the JAK2 mutation. Circumstantial evidence in favor of the model comes from the finding that the JAK2 mutation may be present in some but not all individuals with a familial MPD. The second model postulates that V617F-negative and V617F-positive ET are different diseases (**Figure 1C**; see Color Figures, page 552). Data from analysis of a large ET cohort favors the second model, because there were no significant differences between V617F-positive and V617F-negative ET patients in disease duration or in the frequency of features associated with advanced disease.[7] Moreover, transplantation experiments show that expression of mutant *JAK2* in bone marrow cells is sufficient to cause short-latency erythrocytosis in mice.[4]

Diagnosis

An updated version of the PVSG criteria for the diagnosis of ET is shown in **Table 3**. Using allele-specific PCR on peripheral blood granulocytes the V617F JAK2 mutation is found in approximately 50% of patients with ET.[3,7] A lower proportion of mutation-positive patients was identified by sequencing,[3-6] an observation that reflects the lower sensitivity of the method and the fact that a variable proportion of granulocytes are derived from the malignant clone. In the presence of the JAK2 mutation, a diagnosis of ET still requires excluding other myeloproliferative and related disorders. In the absence of the JAK2 mutation, it is also important to exclude reactive thrombocytosis and iron deficiency.

A number of attempts to develop other new diagnostic tests have been reviewed recently.[24] In patients with ET, X chromosome inactivation patterns are of limited use as a

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Table 3. Proposed diagnostic criteria for essential thrombocythemia (ET).

A1. Platelet count > 600 x 10^9/L for at least 2 months

A2. Acquired JAK2 mutation

B1. No cause for a reactive thrombocytosis
    – e.g., normal inflammatory indices

B2. No evidence of iron deficiency
    – stainable iron in the marrow or normal red cell mean corpuscular volume[a]

B3. No evidence of PV
    – hematocrit < midpoint of normal range or normal red cell mass in presence of normal iron stores

B4. No evidence of chronic myeloid leukemia[b]
    – no Philadelphia chromosome or *bcr-abl* gene rearrangement

B5. No evidence of myelofibrosis
    – no collagen fibrosis and ≤ grade 2 reticulin fibrosis (using 0–4 scale)

B6. No evidence of a myelodysplastic syndrome
    – no significant dysplasia
    – no cytogenetic abnormalities suggestive of myelodysplasia

Diagnosis of ET requires A1+A2+B3–6 (V617F-positive ET) or A1+B1–6 (V617F-negative ET)

[a] If these measurements suggest iron deficiency, PV cannot be excluded unless a trial of iron therapy fails to increase the red cell mass into the polycythemic range (patients need to be monitored closely since a rapid rise in hematocrit can precipitate thrombosis).

[b] Rare patients have chronic myeloid leukemia coexisting with ET or other myeloproliferative diseases.[39]

[c] Approximately 5% of patients with myelodysplastic syndrome carry the V617F JAK2 mutation.

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diagnostic test for two main reasons. Firstly, a clonal pattern (skewed granulocytes and balanced T cells) is found in a significant proportion of normal elderly women and therefore lacks specificity. Secondly, approximately 50% of patients who fulfill clinical criteria for ET have a balanced pattern in their peripheral blood granulocytes suggesting that the majority of these cells are polyclonal. Therefore, the presence of a polyclonal pattern (balanced granulocytes and T cells) in younger women cannot be used to exclude the diagnosis of ET.

Trephine histology has also been suggested as a useful positive diagnostic criterion. It has been reported that patients with ET can be divided into histologically distinct subgroups (true ET, prefibrotic myelofibrosis, and early overt myelofibrosis) with different prognoses.[25] However, megakaryocyte morphology is notoriously difficult to assess in a reproducible manner and detailed studies of interobserver variation are lacking. It is, therefore, not yet clear whether this sort of histological classification is robust enough to be applied widely outside specialized centers, and the inclusion of trephine biopsy histology in the WHO criteria is regarded by many as controversial.

A number of studies have investigated the possibility that the presence of thrombopoietin (TPO)-independent megakaryocyte colonies or erythropoietin-independent erythroid colonies (EECs) might be diagnostically useful. However, both assays are laborious, difficult to standardize and only available in a few specialized centers. Moreover, TPO-independent colonies have been reported in patients with reactive thrombocytosis. Serum TPO levels are not helpful since they are normal or raised in a variety of conditions associated with a high platelet count, including reactive thrombocytosis, ET and other MPDs. Reduced expression of MPL, the TPO receptor, has been reported in patients with ET by some groups but not by others. Increased levels of *PRV1* mRNA in peripheral bloods granulocytes has been reported in approximately 50% of patients with ET.

Clinical course

It is not clear whether patients with ET have a reduced life expectancy compared to the general population, and several cohort studies have reported no significant reduction.[10,15] As with PV, thrombotic events are the major complication encountered during follow-up, with hemorrhagic events occurring less commonly. The reported frequency of thrombosis is variable since different studies have included distinct patient populations and have used varying definitions of major and minor vascular events. A number of risk factors for thrombosis have been identified.[15] Several studies have reported that patients > 60 years or with a prior thrombosis are at high risk of thrombosis. The significance of the platelet count is less clear. Major hemorrhage is reported to be more common in patients with platelets $> 1500 \times 10^9/L$. An increased risk of thrombosis has been suggested with platelet counts $> 1000 \times 10^9/L$ at diagnosis

or in patients with a platelet count above the normal range during treatment, but other studies have not found such an association. However, the increased platelet numbers seem likely to be contributing to the thrombotic diathesis in ET patients since aspirin relieves microvascular symptoms in ET, cytoreduction with hydroxyurea reduces the incidence thrombosis in ET[20] and the ECLAP study shows that aspirin reduces the incidence of thrombotic events in PV.

A number of other features have been claimed to correlate with thrombotic complications.[24] These include a clonal pattern of X chromosome inactivation, reduced expression of MPL in bone marrow megakaryocytes and overexpression of *PRV1* in peripheral blood granulocytes. An increased risk of thrombosis may also be associated with antiphospholipid antibodies, heterozygosity for factor V Leiden and a number of cardiovascular risk factors, including hypertension, smoking and hypercholesterolemia. In the longer term, patients with ET may also develop myelofibrosis or AML. The risk of myelofibrosis is difficult to assess from published data partly because different criteria have been used to define myelofibrotic transformation. In one recent study of 195 patients with a median follow-up of 7 years, the incidence of myelofibrosis was 8% at 10 years.[26] The reported incidence of AML/MDS is very variable because most studies are retrospective and involve small numbers of patients with different lengths of follow-up. However, several points do appear to be clear. First, untreated patients can develop AML. A retrospective study of 2316 Italian patients suggested that AML/MDS occurs in approximately 1% of untreated ET patients.[15] Second, patients treated with hydroxyurea alone (and no other cytotoxic agent) display a low incidence of AML/MDS (see below). Third, patients who require more than one cytotoxic agent have an increased risk of AML/MDS. However, it is not clear whether this reflects the combined effect of these drugs or whether it is a consequence of particularly aggressive disease.

Clinical trials

There have been only two prospective randomized studies of the treatment of patients with ET. In the first, 114 high-risk patients (age > 60 years or prior thrombosis) were randomized to receive hydroxyurea or no cytoreductive agent.[20] Patients with a platelet count $> 1500 \times 10^9/L$ were excluded. During a median follow up period of 27 months, patients on hydroxyurea developed significantly fewer thrombotic events ($P = 0.003$). This was the first clear demonstration that cytoreductive therapy reduces thrombotic events in patients with ET.

The second randomized study was the Medical Research Council (MRC) primary thombocythemia-1 (PT-1) trial,[2] in which high-risk patients (prior thrombosis, age > 60 years or platelets $> 1000 \times 10^9/L$) were randomized to receive hydroxyurea plus aspirin or anagrelide plus aspirin. With over 800 patients randomized and with central clinical and histological review of end-points, it is the largest

and most comprehensive study of essential thrombocythemia performed to date. The results demonstrate several major differences between the two arms. Compared to hydroxyurea plus aspirin, treatment with anagrelide plus aspirin was associated with increased rates of arterial thrombosis, major hemorrhage, myelofibrotic transformation and treatment withdrawal, but a decreased rate of venous thromboembolism.

It is informative to compare these results with the previous Italian study.[20] The actuarial rate of first thrombosis at 2 years was 4%, 8% and 26% for patients receiving hydroxyurea +/- aspirin (both studies), anagrelide plus aspirin (PT-1) or no cytoreductive therapy (Italian study). Notwithstanding the difficulties of such comparisons these data suggest that anagrelide plus aspirin provides partial protection against arterial thrombosis.

In marked contrast to arterial thrombosis, the rate of venous thrombosis was significantly lower in the anagrelide plus aspirin arm. The incidence of venous thrombosis in untreated patients with high-risk essential thrombocythemia is unknown and so it is not clear whether this rate is increased by hydroxyurea plus aspirin or decreased by anagrelide plus aspirin. The optimal management of a patient with prior venous thrombosis will depend on individual circumstances, remembering that arterial thrombotic events are > 3 fold more common than venous thrombotic events in ET.

The different rates of thrombosis in the two arms of PT-1 is intriguing given the equivalent long-term control of the platelet count. These data imply that, in addition to lowering the platelet count, hydroxyurea or anagrelide may modulate thrombosis by other mechanisms (e.g., altered white cell count or function; altered endothelial function). The unexpected increase in major hemorrhage observed in patients receiving anagrelide plus aspirin may reflect an ability of anagrelide to interfere with platelet function in a way that synergizes with low-dose aspirin. Anagrelide blocks platelet phosphodiesterase activity[27] and at high doses (0.5-10 mg/kg) inhibits thrombus formation in animal models.[28] Although most assays of platelet function are normal in patients with essential thrombocythemia receiving anagrelide, some subtle effects on platelet function have been reported.[29,30] The PT-1 results suggest that, if anagrelide is used, the decision whether to use concurrent aspirin should depend on the relative risk of arterial thrombosis and hemorrhage in each individual patient.

Patients receiving anagrelide plus aspirin experienced an increased rate of transformation to myelofibrosis compared to patients receiving hydroxyurea plus aspirin. It is important to emphasize that a diagnosis of myelofibrotic transformation required not only a trephine biopsy showing ≥ grade 3 fibrosis, but also the development of other clinical or laboratory evidence of transformation, which was absent at trial entry. The higher rate of myelofibrotic transformation was not an artifact of the precise definition used, since making the diagnostic criteria more stringent

did not affect the statistical significance. It is possible that the results reflect a chance excess of "prefibrotic form of myelofibrosis" in the anagrelide arm. However, PT-1 is a large randomized trial and the probability that the results can be explained by such a chance occurrence is 1 in a 100 (*P* value was 0.01). The incidence of myelofibrosis in untreated essential thrombocythemia is unknown, and so it is not clear whether the observed differences reflect a protective effect of hydroxyurea or an acceleration of myelofibrosis by anagrelide. Hydroxyurea has been reported to reduce reticulin fibrosis in a variety of myeloproliferative disorders, including essential thrombocythemia.[31,32] On the other hand, anagrelide blocks megakaryocyte differentiation, and the resultant relative increase in immature forms could conceivably result in altered production of profibrotic cytokines.[33,34]

Interestingly, analysis of the response to therapy and complications in the PT-1 trial by JAK2 mutation status revealed that V617F-positive patients were much more sensitive to hydroxyurea.[7] Compared to V617F-negative patients, they required substantially lower doses of hydroxyurea and yet had greater reductions in platelet counts, white cell counts and hemoglobin levels. No such effect was seen in patients receiving anagrelide. Furthermore, the rate of arterial thrombosis appeared to be lower in V617F-positive patients receiving hydroxyurea compared to those receiving anagrelide, an effect that was not evident in V617F-negative patients.

Taken together the results of the PT-1 trial suggest that hydroxyurea plus aspirin should remain first-line therapy for patients with essential thrombocythemia at high risk of developing vascular events. For other patients at a lower risk of thrombosis, the situation is less clear. The decision whether or not to use a cytoreductive agent requires balancing two opposing risks, both of which are small: the risk of a thrombotic event and the risk of a significant drug-related side effect. Unfortunately, the frequency of these two types of events is not clear from existing data. Some studies suggest that patients aged < 60 years and with no prior thrombosis do not exhibit an increased frequency of thrombosis compared to controls.[35] However, the number of patients studied was small, the number of events very small and the choice of an appropriate control population is difficult. Moreover, other studies have found that such patients do have a significant risk of thrombosis.[36] With respect to the risks of treatment, these differ for the different agents. The most commonly used drugs are hydroxyurea, anagrelide and interferon.

Hydroxyurea: Hydroxyurea has emerged as first-line therapy for high-risk patients because of its efficacy, low cost and rare acute toxicity. The main side effects are leg ulcers, a variety of other skin conditions (including photosensitivity and solar keratosis) and reversible bone marrow suppression. A common concern is whether hydroxyurea might be leukemogenic. It is apparent that some cytotoxic drugs such as ^{32}P and chlorambucil are leukemogenic. How-

ever, hydroxyurea has a distinct mechanism of action and does not increase the frequency of acquired mutation in adults with an MPD or sickle cell disease.[37] Some studies have reported that 5%-10% of patients receiving hydroxyurea develop AML/MDS. However, these involved small numbers of patients, many of whom had also received other cytoreductive agents. Patients who receive more than one cytotoxic agent do have a significantly higher risk of developing AML/MDS, although is not clear whether this association reflects an effect of the drugs or a consequence of aggressive disease. By contrast, there are now a number of studies which show that ET patients receiving hydroxyurea alone have a low incidence of AML/MDS (3%-4%)[38-40] and there are no data to show that this incidence is significantly different from that observed in untreated patients. Moreover, follow-up of patients receiving hydroxyurea for sickle cell disease over the past 10 years also suggests that its leukemogenic potential is very low.

Anagrelide: Anagrelide is an imidazo quinazoline derivative originally developed as an inhibitor of platelet aggregation.[15] It was subsequently shown to lower the platelet count in a species-specific manner and at doses lower than that which inhibit platelet aggregation. It is effective at reducing the platelet count (to < 600) in 70%-80% of patients, but approximately 10% are completely refractory, perhaps because of an inability to generate an active metabolite. It is a phosphodiesterase inhibitor and acts as a vasodilator and a positive inotrope. Acute side effects include headaches, palpitations and fluid retention. The PT-1 study shows that anagrelide is not as effective or as well tolerated as hydroxyurea and should not be used as first-line therapy in high-risk patients.

Interferon: Interferon-α is effective at reducing the platelet count below 600×10^9/L in approximately 90% of patients with an average dose of 3 million international units per day. It is not known to be teratogenic or leukemogenic, does not cross the placenta and is often the treatment of choice during pregnancy. However, the need for parenteral administration and its acute side effects, particularly flu-like symptoms, are significant problems and result in treatment withdrawal in a substantial proportion of patients.

Management recommendations

An outline of a risk-stratified approach to the management of ET is presented in **Table 4**. The MRC PT1 trial demonstrates that hydroxyurea should be first-line therapy for most patients with high-risk disease. Interferon-α and anagrelide are both reasonable second-line agents. A decision whether to use concomitant aspirin with anagrelide will require an assessment of the potential risks and benefits in each individual patient. The combination of hydroxyurea and anagrelide can be useful as a way of minimizing side effects associated with the two drugs. The optimal management of a patient with prior venous thrombosis will depend on individual circumstances, remembering

Table 4. Recommendations for management of patients with essential thrombocythemia (ET).

1. All patients:
   – manage reversible cardiovascular risk factors aggressively (e.g., smoking, hypertension, hypercholesterolemia, obesity)

2. High-risk patients (prior thrombosis or age > 60 years or platelets > 1500 x 10^9/L):
   – low-dose aspirin plus hydroxyurea (anagrelide or interferon-α second line)

3. Intermediate-risk patients (age 40–60 years, no high-risk features):
   – either enter into randomized trial (e.g., PT-1 intermediate risk arm)
   – or low-dose aspirin (consider cytoreduction if other cardiovascular risk factors present)

4. Low-risk patients (age < 40 years and no high-risk features):
   – low-dose aspirin

that arterial thrombotic events during follow-up are > 3-fold more common than venous ones in ET.

There is a general consensus that patients at particularly low risk of thrombotic events (age < 40 years, no high-risk features) should receive low-dose aspirin alone (or equivalent). For the remaining intermediate-risk patients (age 40-60 years, no high-risk features), there are no good data to guide management and it is not clear whether cytoreduction is beneficial. Where possible such patients should be entered into a randomized trial such as the ongoing intermediate-risk PT-1 randomization (hydroxyurea plus aspirin versus aspirin alone). There are few data to guide the management of ET in pregnancy.[24] It seems reasonable for patients to receive low-dose aspirin, but the decision whether to lower the platelet count is more contentious and there are conflicting reports as to whether the established factors for thrombosis in non-pregnant patients can predict poor pregnancy outcome. In the absence of clear data, it seems advisable to limit the use of platelet-lowering agents to patients thought to be at high risk of thrombosis and particularly to patients with a history of previous thrombosis or fetal loss. Anagrelide and hydroxyurea should be avoided because of the possibility of teratogenic effects, although there have been reports of normal pregnancies despite exposure to hydroxyurea. Interferon-α is generally regarded as the treatment of choice and should be combined with heparin in patients at particularly high risk, with treatment continuing for several weeks postpartum.

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Author's Note: Unfortunately, it has not been possible to cite many important primary papers because of a limit on the number of references. The author has therefore cited reviews that contain the primary references.

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