Chapter 3
Essential Thrombocythemia

Guido Finazzi

3.1 Introduction

Essential thrombocythemia (ET) is currently classified as a myeloproliferative disorder (MPD), which is a heterogeneous category of clonal stem cell diseases that also includes polycythemia vera (PV), myelofibrosis with myeloid metaplasia (MMM), chronic myeloid leukemia (CML), and atypical MPDs (1). A major advance in our understanding of the pathogenesis of MPDs was made with the recent identification of the V617F JAK2 mutation in a substantial proportion of patients, especially with PV (2–7). This discovery has had a major impact on disease classification, diagnostic approach, and in addressing research strategies in these disorders.

Among the classic MPDs (1), ET shows a longer median survival as well as lower transformation rates into acute myelogenous leukemia (AML). However, the clinical course of ET is complicated by thrombotic and hemorrhagic episodes that occur more frequently in older patients and those with previous vascular events. There is an ongoing debate as to whether the evolution to AML is part of the natural history of the disease or is related to the use of cytoreductive agents given to control the myeloproliferation and avoid vascular complications. Hence, the best strategy is to limit the use of cytotoxic therapy by stratifying patients on the basis of their risk for developing vascular events.

This chapter reviews recent progress in the management of ET with particular emphasis on four key areas: pathogenesis, diagnostic criteria, clinical course, and risk-adapted therapy.

3.2 Pathogenesis

Essential thrombocythemia is thought to result from transformation of a multipotent hematopoietic progenitor. This concept was originally proposed by Fialkow and colleagues, who demonstrated a clonal pattern of X inactivation in multiple myeloid lineages but not in lymphoid cells (8). Subsequent studies in ET have demonstrated

S.M. Ansell (ed.), *Rare Hematological Malignancies.*

that a significant proportion of ET patients do not appear to have clonal hematopoiesis (9, 10). This observation, however, might reflect the limited ability of current techniques to detect a small proportion of clonally derived cells in a background of polyclonal hematopoesis since a recent study has demonstrated the presence of JAK2 V617F in the majority of patients with "polyclonal" ET (11).

Cytogenetic studies have not been helpful. Almost 95% of ET patients have normal cytogenetics and, when present, karyotypic abnormalities are highly variable (12). A clue to the nature of the underlying defect came from the realization that as in PV, hematopoietic progenitors from many patients with ET are hypersensitive to cytokines such as thrombopoietin or erythropoietin (13–15). These observations focused attention on cytokine signal transduction pathways.

In 2005, an identical acquired mutation of JAK2 has been found in the vast majority of patients with PV, as well as approximately half those with ET and MMM (2–7). The mutation (V617F) is located in the negative regulatory JH2 domain and replaces a highly conserved valine with a bulky phenylalanine. As predicted by previous structural and biochemical studies, the consequence of this mutation is increased tyrosine kinase acytivity of JAK2. JAK2 plays a central role in signal transduction from multiple growth factors, and so its activation is consistent with the growth-factor-independent phenotype. Sequence analysis of peripheral blood granulocytes detected the mutation in 12–40% of patients with ET (2–5), but over 50% were positive by allele-specific polymerase chain reaction (PCR) (3). These results demonstrate that ET can be divided into JAK2-positive and JAK2-negative subgroups. The molecular basis for JAK-2-negative ET remains obscure. It is also unclear how the same mutation can give rise to PV, ET, MMM, and other atypical MPDs. Potential explanations include differences between individuals with respect to genetic background, additional acquired mutations, or the target cell for transformation (16).

3.3 Diagnostic Criteria

Also in the current JAK2 V617F era, there is no single clinical or laboratory finding that permits a diagnosis of ET. Thus, the diagnosis must be reached by a mix of positive criteria in conjunction with the exclusion of other myeloproliferative or myelodysplastic disorders as well as conditions that are associated with a reactive thrombocytosis. This principle was used in the diagnostic criteria developed by the World Health Organization (WHO) (17) (Table 3.1).

3.3.1 Platelet Count

The current criteria for ET require a persistent platelet count of $>600 \times 10^9$/L. However, it has been suggested that the platelet count criterion should be reduced to $>400 \times 10^9$/L because, in long-term follow-up studies, the clinical course of

Table 3.1 WHO diagnostic criteria for essential thrombocythemia

Positive criteria

1. Sustained platelet count >600 × 10^9/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakayocytes

Criteria of exclusion

No evidence of PV

- Normal red cell mass or Hb < 18.5 g/dL in men, 16.5 g/dL in women
- Stainable iron in bone marrow, normal serum ferritin, or normal MCV
- If the former condition is not met, failure of iron trial to increase red cell mass or Hb levels to the PV range.

2. No evidence of CML
   - No Philadelphia chromosome and no BCR/ABL fusion gene
3. No evidence of myelodysplastic syndrome
   - No del(5q), t(3;3)(q21;q26), inv(3)(q21q26)
   - No significant granulocytic dysplasia, few if any micromegakaryocytes
4. No evidence that thrombocytosis is reactive due to:
   - Underlying inflammation or infection
   - Underlying neoplasm
   - Prior splenectomy

MCV: Mean cell volume. Source: Adapted from Ref. 17.

patients with platelet counts between 400 10^9/L and 600 × 10^9/L was found to be indistinguishable from that of patients with a clearly diagnosed ET (18, 19). The major problem with this approach is that lowering the threshold of platelet count will improve the sensitivity but reduce the specificity of ET diagnosis. Therefore, the selection of a cutoff of 600 × 10^9/L is probably the most appropriate for the selection of ET patients to be put in therapeutic trials. In the current clinical practice, a lower platelet count can be taken for an initial screening, but this should be supported by other clinical and laboratory ET features.

3.3.2 JAK2 Mutation

The V617F JAK2 mutation is detectable in 40–60% of ET patients ([2–7) and the technology required to detect it is very simple, being generally PCR based (20). Hence, for those patients presenting with an isolated thrombocytosis, or with clinical findings suspicious for a MPD [e.g., patients presenting with Budd Chiari syndrome (21)], a positive screen for V617F JAK2 will confirm the diagnosis as a MPD. The traditional difficulty in making a diagnosis of ET has been excluding a

reactive thrombocytosis in those patients with other comorbidities. This distinction will be simpler in patients with detectable V617F JAK2 but does not, of course, preclude careful clinical history and examination. For V617F JAK2-negative patients, the diagnosis will rely on the WHO criteria (17). A proposed diagnostic scheme including JAK2 mutation screening is reported in Table 3.2 (22).

3.3.3 Bone Marrow Biopsy

It has been suggested that ET can be positively diagnosed by careful, quantitative examination of the bone marrow biopsy (23): this forms the basis of a positive marker for ET in the WHO diagnostic criteria (17). Typical clustering of enlarged megakaryocytes with multilobated nuclei has been advocated to represent the hallmark feature of the disease. The background hematopoiesis in ET is characterized by a discrete pattern of minimal or no hyperplastic erythropoiesis, no change in granulopoiesis, almost no fibrosis, and a reduction of stainable iron. A detailed evaluation of bone marrow features might also help to distinguish "true" ET from the initial stages of MMM, PV, or myelodysplasia. "Early" myelofibrosis is characterized by increasing cellularity with prominent neutrophil granulopoiesis,

Table 3.2 Proposed diagnostic criteria for essential thrombocythemia including JAK2 V617F mutation

A
1. Platelet count $>600 \times 10^9$/L for >2 months
2. Presence of JAK2 V617F mutation
B
1. No cause for a reactive thrombocytosis
2. No evidence of iron deficiency
3. No evidence of PV
- Normal red cell mass or haematocrit <40%
4. No evidence of myelofibrosis
- Collagen fibrosis of the bone marrow absent or less than one-third of the biopsy area without both marked splenomegaly and a leukoerythroblastic blood film
5. No evidence of CML
- No Philadelphia chromosome and no BCR/ABL fusion gene
6. No evidence of myelodysplastic syndrome
- No del(5q), t(3;3)(q21;q26), inv(3)(q21q26)
- No significant granulocytic dysplasia, few if any micromegakaryocytes

Note: Diagnosis of ET requires either A1, A2 and B3-6 or A1 and B1-6.

Source: Adapted from Ref. 22.

borderline to slight reticulin fibrosis, and pronounced abnormalities of megakaryocyte differentiation, including hyperchromasia and marked nuclear-cytoplasmatic deviation. Notably, patients with these morphological features frequently develop an overt myelofibrosis and have a significantly worse life expectancy. However, an experienced observer and a well-standardized procedure are required to diagnose ET by examination of the bone marrow biopsy.

3.3.4 Other Criteria

Some authors have shown that endogenous erythroid colonies or culture examining CFU-Mk (megakaryocytic colony-forming unit) growth might be reliable markers of the disease (13, 24). However, these investigations are not widely available, are expensive, and are technically demanding and, therefore, might be suitable for research purposes or in the occasional patient but not for general use.

Nonstimulated metaphases obtained from marrow aspirates should be examined for cytogenetic abnormalities. This is primarily important in order to exclude the presence of the Philadelphia (Ph) chromosome, the genotypic hallmark of CML, particularly in those patients with very high platelet counts (25). Karyotypic abnormalities generally arise upon transformation of ET to acute leukemia when deletions or elongations of the short arm of chromosomes 1, 2, 5, 17, 20, and 21 are the most frequent defects (12).

3.4 Clinical Course

3.4.1 Frequency

According to population-based epidemiological studies (26, 27), the incidence rates of ET range from 15 to 25 cases per million inhabitants annually. These figures are in agreement with a recent systematic screening for erythrocytosis and thrombocytosis in 10,000 consecutive persons living in the city of Vicenza, Italy (28). This cross-sectional study of healthy people led to the identification of four cases of ET (platelet count $\geq 600 \times 10^9$/L) with an estimated prevalence of 400 cases per million inhabitants (95% confidence interval 109–1020/million). Interestingly, no thrombotic or hemorrhagic complications occurred over 5 years of follow-up in these incidentally discovered ET patients.

The disorder appears to affect primarily middle-aged people, with an average age at diagnosis of about 55 years (29). There is a higher prevelence of females (26, 29), mainly due to a second peak frequency at around 30 years of age for women. This predisposition of young women to develop ET is relevant for the issue of pregnancy discussed below.

3.4.2 Incidence and Type of Major Thrombotic and Hemorrhagic Complications

Thrombosis and hemorrhage are the most frequent clinical complications observed in ET patients (30). In uncontrolled studies, reported cumulative rates for thrombosis and hemorrhage during follow-up ranged from 7% to 17% and 8% to 14%, respectively (31). In one study that also evaluated a control population (32), the incidence of thrombotic episodes was 6.6% per patient-year in ET versus 1.2% in control subjects and the rate of major hemorrhagic complications was 0.33% per patient-year in ET versus 0% in controls.

The most frequent types of major thrombosis include stroke, transient ischemic attack, myocardial infarction, peripheral arterial thrombosis, and deep venous thrombosis often occurring in unusual sites, such as hepatic (Budd-Chiari syndrome), portal, and mesenteric veins. In addition to large-vessel occlusions, ET patients might suffer from microcirculatory symptoms, including vascular headaches, dizziness, visual disturbances, distal paresthesia, and acrocyanosis. The most characteristic of these disturbances is erythromelalgia, consisting of congestion, redness, and burning pain to ischemia and gangrene of distal portions of toes and fingers (33). The most frequent bleeding events are hemorrhages from the gastrointestinal tract, followed by hematuria and other mucocutaneous hemorrhages. Hemarthrosis and large muscle hematomas are uncommon.

3.4.3 Risk Factors

Age over 60 and a previous thrombotic event were identified as major risk factors for thrombosis in a controlled study (32) and in an uncontrolled series of patients (34, 35). Additional risk factors have been also recognized: clonal disease, impaired expression of c-*Mpl* in bone marrow megakaryocytes, overexpression of PRV-1, presence of factor V Leiden, and antiphospholipid antibodies were associated with a higher incidence of vascular complications (reviewed in Ref. 31). The risk is increased by the concomitant presence of hypertension, hypercholesterolemia, and smoking, but it should be recognized that these associations are not consistently found in all studies.

Recently, a prognostic role for leukocytosis in MPDs has been advocated. Three large cohort studies have demonstrated that an increased leukocyte count is a novel independent risk factor for both thrombosis and inferior survival in ET (29, 36) and for thrombosis in PV (37). In one study, a correlation between leukocytosis and the V617F JAK2 mutation was reported (36). In ET and PV, in vivo leukocyte activation has been shown to occur and to be associated with signs of activation of both platelets and endothelial cells (38). Platelet activation is increased in ET patients carrying the V617F JAK2 mutation (39). Thus, leukocyte and platelet activation might play a role in the generation of the prethrombotic state that characterizes ET and PV.

The presence of the V617F JAK2 mutation in about 50% of patients with ET raises the question of whether mutated and nonmutated patients differ in terms of thrombotic risk. The largest relevant study on 806 patients suggested that JAK2 mutation was associated with venous but not arterial events (40). An increased risk of thrombosis in JAK2-mutated patients with essential thrombocythemia was also reported by other investigators (41, 42). However, the rate of vascular complications was not affected by the presence of the mutation in two other relatively large studies, including 150 and 130 patients, respectively (11, 43). It is possible that the higher age distribution and hematocrit and leukocyte levels consistently found in mutation-positive patients (11, 40–43) contributed to the apparent association between JAK2 V617F and thrombosis reported in some studies.

Paradoxically, a very high platelet count ($>1500 \times 10^9$/L) was found to be a major predictor of bleeding rather than thrombosis (44). The explanation of this comes from the well-documented impairment of von Willebrand factor (vWF) multimers found both in patients with ET and those with reactive thrombocytosis (30, 44). Large vWF multimers have been found to be decreased in parallel with the degree of thrombocythemia. Moreover, normalization of the platelet count was accompanied by restoration of a normal plasma vWF multimeric distribution and correction of bleeding tendency. However, in a retrospective study of 99 consecutive young patients (aged <60 years) who presented with extreme thrombocytosis (platelet count $\geq 1000 \times 10^9$/L) and without a previous history of thrombohemorrhagic complications, the incidences of major thrombosis and hemorrhage during the follow-up were similar between those who were treated with prophylactic cytoreductive therapy and those who did not receive such therapy (45). This clinical observation challenges the role of extreme thrombocytosis as a major risk factor for vascular events in otherwise low-risk patients with ET.

3.4.4 Progression of the Disease

Essential thrombocythemia might transform to MMM or acute leukemia (AL) as part of the natural history. In a series of 195 patients followed for a median of 7.2 years (range: 1.9–24), conversion to MMM was observed in 13 cases, with an actuarial probability of 2.7% at 5 years, 8.3% at 10 years, and 15.3% at 15 years (46). In a long-term cohort study of 322 consecutive patients followed for a median of 13.6 years life expectancy, survival was similar to that of the control population in the first decade of disease [risk ratio: 0.72; 95% confidence interval (CI): 0.50–0.99) but became significantly worse thereafter (risk ratio: 2.21; 95% CI: 1.74–2.76)]. Multivariable analysis identified age at diagnosis of 60 years or older, leukocytosis, tobacco use, and diabetes mellitus as indendent predictors of poor survival. The risk of leukemic or any myeloid disease transformation was low in the first 10 years (1.4% and 9.1%, respectively) but increased substantially in the second (8.1% and 28.3%, respectively) and third (24.0% and 58.5%, respectively) decades of the disease (43).

3.5 Risk-Adapted Therapy

Before deciding whether to start platelet-lowering treatment, ET patients should be evaluated for history of thrombotic or hemorrhagic events and the presence of cardiovascular risk factors (i.e., smoking, hypertension, hypercholesterolemia, and diabetes). Then they should be stratified according to their probability of developing major bleeding or thrombosis (Table 3.3)(1, 47).

3.5.1 Low Risk

Avoiding cytoreduction is an option for low-risk ET patients. The natural history of such patients left untreated was prospectively evaluated in a controlled study that compared 65 low-risk patients with 65 age- and sex-matched normal controls (48). After a median follow-up of 4.1 years, the incidence of thrombosis was not significantly higher in patients than in controls (1.91% vs. 1.5% per patient-year; age- and sex-adjusted risk ratio: 1.43; 95% CI: 0.37–5.4). No major bleeding was observed. Thrombotic deaths seem very rare in low-risk ET subjects, and there are no data indicating that fatalities can be prevented by starting cytoreductive drugs early. Therefore, withholding chemotherapy might be justifiable in young, asymptomatic ET patients with a platelet count below $1{,}500 \times 10^9$/L. This policy is based on the low risk of complications and the potential leukemogenicity of cytotoxic drugs. However, the strength of these recommendations is based on studies with small number of patients, and further data from large clinical trials are needed.

Aspirin at different doses (30–500 mg/day) has been found to control microvascular symptoms, such as erythromelalgia, and transient neurological and ocular disturbances (TIAs), including dysarthria, hemiparesis, scintillating scotomas, amaurosis fugax, migraines, and seizures (33). The efficacy and safety of aspirin, 100 mg daily, in preventing major thrombotic events has been formally assessed in a randomized clinical trial in PV (49). Aspirin lowered significantly the risk of a primary combined

Table 3.3 Classification of essential thrombocythemia based on thrombotic and hemorrhagic risk

Low risk	Age < 60 years, and
	No history of thrombosis or major bleeding, and
	Platelet count < 1500 x 10^9/L
Intermediate risk	Neither low risk nor high risk
High risk	Age > 60 years, or
	A previous history of thrombosis or major bleeding

Note: Correction of cardiovascular risk factors (smoking, hypertension, hypercolesterolemia, diabetes) is recommended in all patients; their contribution to thrombotic risk classification is controversial (see text).

Source: Adapted from Ref. 1.

endpoint, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and major venous thromboembolism (relative risk: 0.4; 95% CI: 0.18–0.91, $p = 0.0277$) without increasing major bleeding (relative risk: 1.6; 95% CI: 0.27–9.71). Based on these findings, an antithrombotic preventive strategy with low-dose aspirin is recommended in all PV patients. Translating evidence from this study to ET can be considered, but formal clinical trials have not hitherto been produced.

3.5.2 Intermediate Risk

Whether some patients might be classified as at "intermediate risk" of thrombosis is more contentious. The rationale for assigning this risk category is the increase in incidence of thrombotic events in the age range 40–60 years compared to less than 40 years (32) and the uncertainty over the weighting that might be ascribed to weaker or more controversial risk factors. The Italian Consensus Criteria define "intermediate risk" as age 40–60 years, platelets less than 1000×10^9/L, and either vascular risk factors or familial thrombophilia with no consensus on treatment (31). In a recent review, Elliott and Tefferi suggested that those aged 60 years, with no history of thrombosis and either a platelet count 1500×10^9/L or cardiovascular risk factors (e.g., smoking, diabetes) are of intermediate risk and should be treated with aspirin, but they concluded there was no consensus on cytoreductive therapy (30). Finally, in the United Kingdom, intermediate-risk patients, aged 40–60 years with all of the following: platelets less than 1500×10^9/L, no prior thrombosis or hemorrhage, no hypertension or diabetes, are entering into an ongoing randomized study comparing HU plus aspirin or aspirin alone (50).

3.5.3 High Risk

3.5.3.1 Hydroxyurea

Hydroxyurea (HU) has emerged as the treatment of choice in high-risk patients with ET (Table 3.3) because of its efficacy in preventing thrombosis (see Section 3.5.3.4) and rare acute toxicity. Hematopoietic impairment, leading to neutropenia and macrocytic anemia, is the main short-term toxic effect of HU. Other less frequent side effects include oral and leg ulcers and skin lesions.

The leukemogenicity of this agent is still debated. Some long-term studies found that a proportion of ET patients treated with HU developed acute leukemia (51, 52). In other studies, however, this drug was rarely associated with secondary malignancies when used alone (53–56). In an analysis of 25 ET patients younger than 50 years and treated with HU for a high risk of thrombosis, no leukemic or neoplastic transformation occurred after a median follow-up of 8 years (range: 5–14) (53). In 1638 patients with PV enrolled in a prospective study, HU alone did not enhance the

risk of leukemia in comparison with patients treated with phlebotomy only (hazard ratio: 0.86; 95% CI: 0.26–2.88; $p = 0.8$), whereas this risk was significantly increased by any other cytoreductive drug, namely radiophosphorus, busulphan, or pipobroman, either used alone or in combination (hazard ratio: 5.46; 95% CI: 1.84–16.25; $p = 0.002$) (54). The incidence of acute leukemic transformation is higher in patients with ET treated with HU if they have cytogenetic abnormalities (51, 52) or have received other cytotoxic drugs with different mechanisms of action (51, 54–56).

3.5.3.2 Anagrelide

Anagrelide, an imidazo quinazinoline derivative, has been shown to reduce the platelet count in a species-specific manner (57, 58). The mechanism by which anagrelide induces thrombocytopenia is unclear, but current attention is focused on inhibition of megakaryocytes differentiation and maturation (58). Major side effects of the drug include palpitations, headaches, noncardiac edema, and congestive cardiac failure (58). In one report, patients treated with anagrelide developed cardiomyopathy (59).

There is extensive experience with the use of this drug, which is licensed in United States as a first-line agent by the Food and Drug Administration for control of thrombocytosis associated with any myeloproliferative disorders. In Europe, the drug has been granted a license only for ET patients refractory to or intolerant of first-line therapy. The criteria for defining resistance or intolerance to HU have been recently established by an International Working Group (60). They include the following: platelet count greater than 600×10^9/L after 3 months of at least 2 g/day of HU (2.5 g/day in patients with a body weight over 80 kg); platelet count greater than 400×10^9/L, and white blood count (WBC) less than 2.5×10^9/L or Hb less than 10 g/dL at any dose of HU; presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of HU; and HU-related fever.

Until recently, studies of anagrelide in ET were nonrandomized, lacked a control arm, and had relatively limited follow-up. The largest study to date evaluated 934 ET patients for efficacy and 2251 for safety and had a maximum follow-up of 7 years; there was no evidence that anagrelide increased conversion to AL and no mention was made of myelofibrosis (61). A study of 35 consecutive young ET patients treated with anagrelide, with a median follow-up of 10.7 years, demonstrated that 20% had thrombotic complications and a similar proportion had major hemorrhagic complications, raising a question about the efficacy of anagrelide (62). These events occurred when the platelet count was above 400×10^9/L suggesting that control of the platelet count to below 400×10^9/L might reduce this risk. A second major finding from this study was the development of a significant anemia of more than 3g/dL in a quarter of patients.

3.5.3.3 Interferon-alpha

Interferon (IFN)-α has been evaluated in several cohorts of ET patients (reviewed in Ref. 63). Platelet count was reduced to below 600×10^9/L in about 90% of cases

after about 3 months, with an average dose of 3 million international units (IU) daily. The time and degree of platelet reduction during the induction phase were dose dependent. The IFN-α dose can be tapered during maintenance, but after its discontinuation, the platelet count rebounds in the majority of patients. IFN-α is not known to be teratogenic and does not cross the placenta. Thus, it has been used successfully throughout pregnancy in some ET patients with no adverse fetal or maternal effects.

Side effects are a major problem with this drug. In addition to flulike symptoms observed in the early treatment phase, signs of chronic toxicity include weakness, myalgia, weight and hair loss, gastrointestinal toxicity, and depression. In a series of 273 ET patients (63), IFN-α therapy was terminated in 25% (67 cases) before completion of the treatment. The rate of withdrawal ranged between 0% and 66% in the different studies. This wide range might be partly explained by the difference in observation times that ranged from 1 month to 4 years. So far, no leukemogenic effects have been reported.

Recently, semisynthetic pegylated forms of interferon-α (peg-IFN-α) have been used to treat ET, which in a limited number of studies (reviewed in Ref. 64) have been shown to be superior to unmodified IFN as related to its adverse event profile and efficacy. Interestingly, the use of peg-IFN-α-2a in 27 patients with PV was able to decrease the percentage of mutated JAK2 allele in 24 cases (89%), from a mean of 49% to a mean of 27% (65). However, a more limited effect on JAK2 mutational status of another form of peg-IFN-α (peg-IFN-α-2b) in patients with PV and ET has been reported (66). Despite its high cost and toxicity, IFN remains a useful agent in cytoreductive treatment of ET, especially in very young patients and pregnant women.

3.5.3.4 Clinical Trials

Two randomized clinical trials assessing benefits and risks of myelosuppressive therapy in ET patients at high risk of thrombosis have been carried out so far. The first was performed about 10 years ago in Italy and evaluated HU versus untreated controls (67): 114 ET patients were randomized to HU or no cytoreductive treatment. During a median follow-up of 27 months, 2 thromboses were recorded in the HU-treated group (1.6%/patient-year) compared with 14 in the control group (10.7%/patient-year; $p = 0.003$). This study provided the basis for considering HU as the standard therapy for high-risk ET patients and the reference arm for other randomized trials.

The second trial was carried out in United Kingdom and compared HU plus aspirin with anagrelide plus aspirin in 809 high-risk ET patients analyzed with a median follow-up of 39 months (68). Overall, patients randomized to anagrelide and aspirin were more likely to reach the composite primary endpoint of major thrombosis (arterial or venous), major hemorrhage, or death from a vascular cause ($p = 0.03$). When individual endpoints were assessed, arterial thrombosis, major hemorrhage, and myelofibrosis were all significantly more frequent for patients treated with

anagrelide ($p = 0.004$, 0.008, and 0.01 respectively). However anagrelide and aspirin seems to offer at least partial protection from thrombosis, as the prevalence of thrombotic events was significantly lower than the control arm of the Italian study (67) (actuarial rate of first thrombosis 8% versus 26% at 2 years, respectively), whereas the HU arms were approximately equivalent (actuarial rate of first thrombosis 4% at 2 years in both trials). The success of HU is likely to reflect the importance of additional factors such as the hematocrit, leukocyte count, or subtle effects on the endothelium in the pathogenesis of thrombosis. Intriguingly, venous thrombosis was, however, less frequent in patients treated with anagrelide ($p = 0.006$).

Major hemorrhage was increased for anagrelide plus aspirin treatment ($p = 0.008$). The most frequent of these endpoints were gastrointestinal hemorrhages. Hemorrhagic events might result from some subtle effect on platelet function, possibly accentuated by aspirin or in relation to combined gastric toxicity.

Myelofibrotic transformation was seen in 16 patients treated with anagrelide in comparison with 5 with HU. It seems logical that anagrelide might be less effective than HU at suppressing the natural evolution of ET to myelofibrosis, as the number of megakaryocytes remains elevated in ET patients treated with anagrelide compared to those given HU. There is also evidence that despite control of the platelet count, levels of tranforming growth factor-β remain elevated in patients treated with anagrelide (69). The incidence of myelofibrosis in the anagrelide arm (3.95%) at median follow-up of 39 months is approximately in accordance with what has previously reported (0.9% per annum) (46), supporting the view that HU might be more effectively suppressing myelofibrosis.

3.5.4 Pregnancy

Essential thrombocythemia is unique among the other Philadelphia negative MPDs, as it is relatively common among women of child-bearing age (70). In a recent systematic review of the literature, outcome data from 461 pregnancies reported by retrospective and prospective cohort studies were evaluated (31). The rate of spontaneous abortions was 44%, which is about threefold higher than in the general population. Placental infarction was reported in 18 cases: these were often responsible for intrauterine fetal growth retardation (11 cases). Abruptio placentae was reported in nine cases (3.6%), a rate that is higher than in the general population (1%). Maternal complications are relatively rare with no fatalities, but postpartum thrombotic episodes were reported in 13 patients (5.2% of the pregnancies) emphasizing the need for postpartum thrombo-prophylaxis.

The average platelet count at the beginning of pregnancy in patients with successful pregnancies was 1010×10^9/L, whereas it was 977×10^9/L among those with an unsuccessful outcome (31); thus, the baseline platelet count did not predict pregnancy outcome. During the second trimester, a spontaneous decline was registered to a nadir of 599×10^9/L. In the postpartum period, the platelet counts rose back up to their earlier levels and rebound thrombocytosis occured in some patients.

The apparent low risk of maternal complications must be considered in context, as the majority of these patients are "low-risk" ET. Most pregnant ET patients not in the high-risk category should be treated with aspirin and postpartum prophylaxis with heparin and closely monitored for complications. For those patients with previous pregnancy or disease–related complications (>3 first-trimester or 1 second- or third-trimester loss, severe Intrauterine Growth Retardation (IUGR), preeclampsia, significant hemorrhage or thrombotic event, and/or extreme thrombocytosis) therapeutic options include aspirin, low-molecular-weight heparin, and IFN-α (30,70) (Table 3.4). However, only limited literature to support optimal management strategies is available and there is a need for international collaboration to address these issues and define best care (71).

3.6 Personal Approach to Therapy

My first step in deciding the treatment of a patient with ET is to assess his/her risk of major thrombotic or bleeding complications (Table 3.3). I do not treat patients clearly classifiable as "low risk," but I give low-dose aspirin (100 mg daily) if they present with microvascular symptoms, such as erythromelalgia, paresthesiae or atypical visual disturbances or associated cardiovascular risk factors (Figure 3.1). The management of patients with extreme thrombocytosis (>1500 × 10^9/L) and otherwise low-risk ET is more contentious (45). I favor patient's age and symptoms over platelet count, avoiding cytoreductive therapy in very young (<40 years),

Table 3.4 Risk-adapted management of ET in pregnancy

1. Risk stratification.
   At least one of the following defines high-risk pregnancy:
   - Previous major thrombotic or bleeding complication
   - Previous severe pregnancy complications*
   - Platelet count >1500 × 10^9/L
2. Therapy
   a) Low-risk pregnancy
   - Aspirin 100 mg/day
   - LMWH 4000 U/day after delivery until 6 weeks postpartum

   b) High-risk pregnancy
   As above, plus
   - If previous major thrombosis or severe pregnancy complications: LMWH throughout pregnancy (stop aspirin if bleeding complications)
   - If platelet count >1500 × 10^9/L: consider IFN-α
   - If previous major bleeding: avoid aspirin and consider IFN-α to reduce thrombocytosis

*Note: Severe pregnancy complications: ≥3 first-trimester or ≥1 second- or third-trimester losses, birth weight <5th centile of gestation, preeclampsia, intrauterine death or stillbirth.

LMWH: Low molecular weight heparin.

Source: Adapted from Ref. 70.

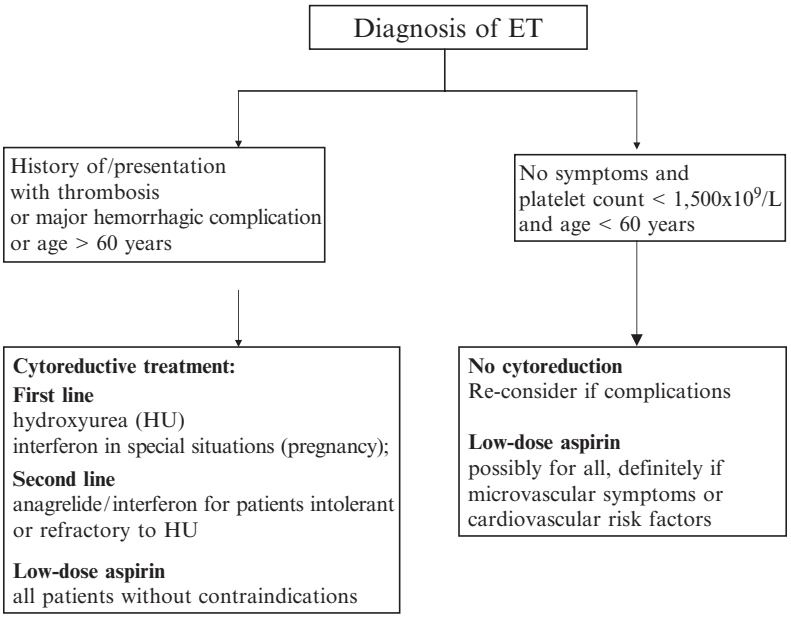

Figure 3.1 An algorithm of risk-adapted treatment recommendations in patients with ET. Classification of intermediate risk is controversial: A randomized study comparing aspirin versus aspirin plus HU in intermediate risk patients is ongoing (see text)

completely asymptomatic patients with stable platelet count also in the range of (1600–1800) × 10^9/L. However, I start therapy in the presence of rapidly increasing platelet counts and/or minor bleeding or vascular disturbances. In patients younger than 40 years of age, my first choice is IFN-α. If the drug is ineffective or not tolerated, I use HU. In patients over 40 years of age with more than 1500 × 10^9/L platelets and in those with definitely "high-risk" ET, the therapy of choice is HU plus low-dose aspirin (47). I consider anagrelide as second-line treatment in high-risk patients intolerant or refractory to HU (60), provided they have a normal cardiac function. I assess JAK2 V617F in all patients with ET, but, for the time being, I do not use the mutation status to decide therapy. It is hoped that molecularly targeted treatment will be available in the near future, as promising JAK2-targeted small molecule drugs are already on the horizon.

References

1. Tefferi A, Barbui T. *bcr/abl* negative, classic myeloproliferative disorders: diagnosis and treatment. Mayo Clin Proc 2005;80:1220–1232.
2. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature 2005;434:1144–1148.

3. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet 2005;365:1054–1061.
4. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell 2005;4:387.
5. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 2005;352: 1779–1790.
6. Zhao R, Xing S, Li Z, et al. Identification of an acquired JAK2 mutation in polycythemia vera. J Biol Chem 2005;280:22,788–22,792.
7. Jones AV, Kreil S, Zoi K, et al. Widespread occurrence of the JAK2 V617 mutation in chronic myeloproliferative disorders. Blood 2005;106:2162–2168.
8. Fialkow PJ, Faguet GB, Jacobson RJ, et al. Evidence that essential thrombocythemia is a clonal disorder with origin in a multipotent stem cell. Blood 1981;58:916–919.
9. el-Kassar N, Hetet G, Briere J, et al. Clonality analysis of hematopoiesis in essential thrombocythemia: advantages of studying T lymphocytes and platelets. Blood 1997;89:128–134.
10. Harrison CN, Gale RE, Machin SJ, et al. A large proportion of patients with a diagnosis of essential thrombocythemia do not have a clonal disorder and may be at lower risk of thrombotic complications. Blood 1999;93:417–424.
11. Antonioli E, Guglielmelli P, Pancrazzi A, et al. Clinical implications of the JAK2 V617F mutation in essential thrombocythemia. Leukemia 2005;19:1847–1849.
12. Steensma DP, Tefferi A. Cytogenetic and molecular genetic aspects of essential thrombocythemia. Acta Haematol 2002;108:55–65.
13. Axelrad AA, Eskinazi D, Correa PN, et al. Hypersensitivity of circulating progenitor cells to megakaryocyte growth and development factor (PEG-rHu MGDF) in essential thrombocythemia. Blood 2000;96:3310–3321.
14. Kawasaki H, Nakano T, Kohdera U, et al. Hypersensitivity of megakaryocyte progenitors to thrombopoietin in essential thrombocythemia. Am J Hematol 2001;68:194–197.
15. Li Y, Hetet G, Maurer AM, et al. Spontaneous megakaryocyte colony formation in myeloproliferative disorders is not neutralizable by antibodies against IL3, IL6 and GM-CSF. Br J Haematol 1994;87:471–476.
16. Schafer AI. Molecular basis of the diagnosis and treatment of polycythemia vera and essential thrombocythemia. Blood 2006;107:4214–4122.
17. Imbert M, Pierre R, Thiele J, et al. Essential thrombocythemia. In: Jaffe ES, Harris NL, Stein H, et al., editors. Pathology and genetics of tumours of hematopoietic and lymphoid tissues. Lyon: IARC Press; 2001. p. 39–41.
18. Lengfelder E, Hochhaus A, Kronawitter U, et al. Should a platelet limit of 600×10^9/l be used as a diagnostic criterion in essential thrombocythemia? An analysis of the natural course including early stages. Br J Haematol 1998;100:15:23.
19. Sacchi S, Vinci G, Gugliotta L, et al. Diagnosis of essential thrombocythemia at platelet counts between 400 and 600×10^9/l. Haematologica 2000;85:492–495.
20. Campbell PJ, Scott LM, Baxter EJ, et al. Methods for the detection of the JAK2 V617F mutation in human myeloproliferative disorders. Methods Mol Med 2006;125:253–264.
21. Patel RK, Lea NC, Heneghan MA, et al. Prevalence of the activating JAK2 tyrosine kinase mutation V617F in the Budd-Chiari syndrome. Gastroenterology 2006;130:2031–2038.
22. Harrison CN, Green AR. Essential thrombocythemia. Best Pract Res Clin Haematol 2006;19:439–453.
23. Thiele J, Kvasnicka HM, Zankovich R, et al. Relevance of bone marrow features in the differential diagnosis between essential thrombocythemia and early stage idiopathic myelofibrosis. Haematologica 2000;85:1126–1134.
24. Westwood NB, Pearson TC. Diagnostic applications of hemopoietic progenitor culture techniques in polycythaemias and thrombocythaemias. Leuk Lymphoma 1996;22(SUppl):95–103.
25. Tefferi A. Ultra high platelet count might be a characteristic feature of chronic myeloid leukemia rather than essential thrombocyhthemia. Leuk Res 2006;Sep 27 [Epub ahead of print].

26. Mesa RA, Silverstein MN, Jacobsen SJ, et al. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County study, 1976–1995. Am J Hematol 1999;61:10–15.
27. Johansson P, Kutti J, Andreasson B, et al. Trends in the incidence of chronic Philadelphia chromosome negative (Ph-) myeloproliferative disorders in the city of Goteborg, Sweden, during 1983–99. J Intern Med 2004;256:161–165.
28. Ruggeri M, Tosetto A, Frezzato M, et al. The rate of progression to polycythemia vera or essential thrombocythemia in patients with erythrocytosis or thrombocytosis. Ann Intern Med 2003;139:470–475.
29. Wolanskyj AP, Schwager SM, McClure RF, et al. Essential thrombocythemia beyond the first decade: life expectancy, long-term complication rates, and prognostic factors. Mayo Clin Proc 2006;81:159–166.
30. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythemia vera and essential thrombocythaemia. Br J Haematol 2005;128:275–290.
31. Barbui T, Barosi G, Grossi A, et al. Evidence- and consensus-based practice guidelines for the therapy of essential thrombocythemia. A statement from the Italian Society of Hematology. Haematologica 2004;89:215–232.
32. Cortelazzo S, Viero P, Finazzi G, et al. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. J Clin Oncol 1990;8:556–562.
33. van Genderen PJ, Michiels JJ. Erythromelalgic, thrombotic and hemorrhagic manifestations of thrombocythaemia. Presse Med 1994;23:73–77.
34. Tefferi A, Fonseca R, Pereira D, et al. A long-term retrospective study of young women with essential thrombocythemia. Mayo Clin Proc 2001;76:22–28.
35. Besses C, Cervantes F, Pereira A, et al. Major vascular complications in essential thrombocythemia: a study of the predictive factors in a series of 148 patients. Leukemia 1999;13:150–154.
36. Carobbio A, Finazzi G, Guerini V, et al. Leukocytosis is a risk factor for thrombosis in essential thrombocythemia: intercation with tratement, standard risk factors and JAK2 mutation status. Blood 2007;109:2310–2313.
37. Landolfi R, Di Coennazo L, Barbui T, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood 2007;109:2446–2452.
38. Falanga A, Marchetti M, Barbui T, et al. Pathogenesis of thrombosis in essential thrombocythemia and polycythemia vera: the role of neutrophils. Semin Hematol 2005;42:239–247.
39. Arellano-Rodrigo E, Alvarez-Larran A, Reverter JC, et al. Increased platelet and leukocyte activation as contributing mechanisms for thrombosis in essential thrombocythemia and correlation with the JAK2 mutation status. Haematologica 2006;91:169–175.
40. Campbell PJ, Scott LM, Buck G, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet 2005;366:1945–1953.
41. Cheung B, Radia D, Pantedelis P, et al. The presence of the JAK2 V617F mutation is associated with higher haemoglobin and increased risk of thrombosis in essential thrombocythaemia. Br J Haematol 2005;132:244–250.
42. Finazzi G, Rambaldi A, Guerini V, et al. Risk of thrombosis in patients with essential thrombocythemia and polycythemia vera according to JAK2 V617F status. Haematologica 2007; 92:135–136.
43. Wolanskyj AP, Lasho TL, Schwager SM, et al. JAK2 V617F mutation in essential thrombocythaemia: clinical associations and long-term prognostic relevance. Br J Haematol 2005;131:208–213.
44. van Genderen PJ, Budde U, Michiels JJ, et al. The reduction of large vonWillebrand multimers in plasma in essential thrombocythemia is related to the platelet count. Br J Haematol 1996; 93:962–965.
45. Tefferi A, Gangat N, Wolanskyj AP. Management of extreme thrombocytosis in otherwise low-risk essential thrombocythemia: does number matter? Blood 2006;108:2493–2494.

46. Cervantes F, Alvarez-Larran A, Talarn C, et al. Myelofibrosis with myeloid metaplasia following essential thrombocythemia: actuarial probability, presenting characteristics and evolution in a series of 195 patients. Br J Haematol 2002; 118:786–790.
47. Barbui T, Finazzi G. When and how to treat essential thrombocythemia. N Engl J Med 2005;85–86.
48. Ruggeri M, Finazzi G, Tosetto A, et al. No treatment for low-risk essential thrombocythemia: results from a prospective study. Br J Haematol 1998;103:772–777.
49. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 2004;350:114–124.
50. Harrison CN, Green AR. Essential thrombocythemia. Hematol Oncol Clin North Am 2003;17:1175–1190.
51. Sterkers Y, Preudhomme C, Lai J-L, et al. Acute myeloid leukemia and myelodyslastic syndromes following essential thrombocythemia treated with hydroxyurea: high proportion of cases with 17p deletion. Blood 1998;91:616–622.
52. Lofvenberg E, Nordenson I, Walhlin A. Cytogenetic abnormalities and leukemic transformation in hydroxyurea-treated patients with Philadelphia chromosome negative chronic myeloproliferative disease. Cancer Genet Cytogenet 1990;49:57–67.
53. Finazzi G, Ruggeri M, Rodeghiero F, et al. Efficacy and safety of long-term use of hydroxyurea in young patients with essential thrombocythemia and a high risk of thrombosis. Blood 2003;101:3749.
54. Finazzi G, Caruso V, Marchioli R, et al. Acute leukemia in polycythemia vera. An analysis of 1638 patients enrolled in a prospective observational study. Blood 2005;105:2664–2670.
55. Finazzi G, Ruggeri M, Rodeghiero F, et al. Second malignancies in patients with essential thrombocythemia treated with busulphan and hydroxyurea: long-term follow-up of a randomized clinical trial. Br J Haematol 2000;110:577–583.
56. Murphy S, Peterson P, Iland H, et al. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival and leukemic transition by treatment. Semin Hematol 1997;34:29–39.
57. Anagrelide study group. Anagrelide, a therapy for thrombocythemic states: experience in 577 patients. Anagrelide Study Group. Am J Med 1992;92:69–76.
58. Wagstaff AJ, Keating GM. Anagrelide. A review of its use in the management of essential thrombocythaemia. Drugs 2006;66:111–131.
59. Jurgens DJ, Moreno-Aspitia A, Tefferi A. Anagrelide-associated cardiomyopathy in polycythemia vera and essential thrombocythemia. Haematologica 2004;89:1394–1395.
60. Barosi G, Besses C, Birgegard G, et al. A unified definition of clinical resistance/intolerance to hydroxyuea in essential thrombocythemia: results of a consensus process by an international working group. Leukemia 2007;24:277–280.
61. Fruchtman SM, Petitt RM, Gilbert HS, et al. Anagrelide: analysis of long term safety and leukemogenic potential in myeloproliferative disorders Leuk Res 2005;29:481–491.
62. Storen EC, Tefferi A Long-term use of anagrelide in young patients with essential thrombocythemia. Blood 2001; 97:863–866.
63. Lengfelder E, Griesshammer M, Hehlmann R. Interferon-alpha in the treatment of essential thrombocythemia. Leuk Lymphoma 1996;22(Suppl 1):135–142.
64. Quintas-Cardama A, Kantarjian HM, Giles F, et al. Pegylated interferon therapy for patients with Philadelphia chromosome–negative myeloproliferative disorders. Semin Thromb Hemost 2006;32:409–416.
65. Kiladjian JJ, Cassinat B, Turlure P, et al. High molecular response rate of polycythemia vera patients treated with pegylated interferon α-2a. Blood 2006;108: 2037–2040
66. Samuelsson J, Mutschler M, Birgegard G, et al. Limited effects on JAK2 mutational status after pegylated interferon α-2b therapy in polycythemia vera and essential thrombocythemia. Haematologica 2006;91:1281–1282.
67. Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea in the treatment of patients with essential thrombocythemia at high risk of thrombosis: a prospective randomized trial. N Engl J Med 1995;332:1132–1136.

68. Harrison CN, Campbell P, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 2005;353:33–45.
69. Lev PR, Salim JP, Kornblihtt LI, et al. PDGF-A, PDGF-B, TGFbeta, and bFGF mRNA levels in patients with essential thrombocythemia treated with anagrelide. Am J Hematol 2005;78:155–157.
70. Harrison C. Pregnancy and its management in the Philadelphia negative myeloproliferative diseases. Br J Haematol 2005;129:293–306.
71. Griesshammer M, Struve S, Harrison C. Essential thrombocythemia/polycythemia vera: the need for a observational study in Europe. Semin Thromb Haemost 2006;32:422–429.