

What is the Standard Treatment in Essential Thrombocythemia

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Abstract

The treatment of patients with essential thrombocythemia (ET) should be based primarily on the expected risk of major thrombotic complications. Although the specific values chosen for separating different risk categories are in part arbitrary, the following recommendations can be made. Young asymptomatic subjects with platelet counts below $1,500 \times 10^9/L$ are at lower risk and can be followed untreated. However, it should be emphasized that thrombotic events can also occur in a small percentage of these lower-risk cases. Low-dose aspirin (100-300 mg/day) should be given to patients with symptoms of microvascular occlusion, such as erythromelalgia or transient neurological attacks, and avoided in those with bleeding manifestations. The risk/benefit of low-dose aspirin in the primary prevention of thrombosis in asymptomatic patients remains uncertain. For high-risk patients (age >60 years, or platelet count $>1,500 \times 10^9/L$, or previous thrombosis), hydroxyurea, plus aspirin in the case of thrombosis, is the treatment of choice because its efficacy in preventing thrombotic complications has been proven in a randomized clinical trial. However, the possible long-term leukemogenicity of this drug, as well as that of other effective cytoreductive agents such as busulphan and pipobroman, remains a major concern. Anagrelide and interferon could overcome this worry but their efficacy has been hitherto demonstrated only in lowering the platelet count. Controlled clinical studies showing a benefit in preventing thrombotic and hemorrhagic complications are urgently needed.

Essential thrombocythemia (ET) is a disorder of the multipotential hemopoietic stem cell leading to bone marrow hyperplasia, excessive proliferation of megakaryocytes and a sustained elevation of the platelet count [1-12]. Current diagnostic criteria are listed in Table 1. ET is generally considered a disease of the middle aged with median onset between the ages of 50 and 60 years and a slight female preponderance. However, with the advent of automated platelet counting, it is now diagnosed with increasing frequency in young people. The major cause of mortality and morbidity are thromboembolic complications, which occur more frequently in older subjects or in those with previous thrombosis. Severe bleeding is rare, nowadays, and limited to patients with very high platelet count. The evolution into leukemia is an unusual occurrence, but there is concern that the rate of transformation may be increased by chemotherapy. Thus, the therapeutic dilemma in ET is balancing the risk of thrombosis, bleeding and leukemic transformation [3]. In this paper, we will review the

therapeutic options currently available for ET patients, taking into account their different risk to develop major thrombotic and bleeding events.

1. Risk Stratification of Patients with ET

ET symptomatic patients usually present with either vascular occlusive or haemorrhagic complications [13]. The vascular occlusive events either occur in the microvasculature, with symptoms such as transient cerebral ischemia, migraine and visual dysfunction [14] digital ischemia and erythromelalgia [15] or in larger vessels usually arterial, although major venous occlusions such as splanchnic vein thrombosis do occur [16] Haemorrhagic events are less frequent than thrombosis and may occur either spontaneously or following trauma. Due to this heterogenous clinical presentation, several studies have focused on the search for factors possibly associated with an increased risk of these complications [17-21]. Unfortunately, despite the identification of a

Table 1.

Updated Diagnostic Criteria of Essential Thrombocythemia [8, modified].

I	Platelet count >600,000/L
II	Hematocrit <0.46, or normal RBC mass (Males <36 mL/kg, females <32 mL/Kg)
III	Stainable iron in marrow or normal serum ferritin or normal RBC mean corpuscular volume*
IV	No Philadelphia chromosome or bcr/abl gene rearrangement
V	Collagen fibrosis of marrow
	A. Absent or
	B. <1/3 biopsy area without both marked splenomegaly and leukoerythroblastic reaction
VI	No cytogenetic or morphologic evidence for a myelodysplastic syndrome
VII	No cause for reactive thrombocytosis

If these measurements suggest iron deficiency, PV cannot be excluded unless a trial of iron therapy fails to increase the RBC mass into the polycythemic range

broad array of specific structural, biochemical and metabolic platelet defects, no parameter of hemostasis has been shown to reliably herald a thrombotic or bleeding tendency in ET patients [22,23]. A major limitation of the available studies is that they are almost all retrospective and based on relatively small numbers of patients. This may explain the wide range in prevalence of haemorrhagic (13% to 63%) and thrombo-embolic (8% to 84%) complications reflecting the referral bias in the reported series.

Hemorrhagic symptoms, which consist of skin bruising, recurrent bleeding from mucous membranes or the digestive tract have been found more frequently in patients with platelet counts in excess of $1,000 \times 10^9/L$ and this may be related to an acquired deficiency of von Willebrand's factor [24,25]. The number of circulating platelets directly affects the concentration of plasma large vWF multimers, which may compromise hemostasis at high platelet counts. Serious bleeding may be spontaneous or triggered by contemporaneous aspirin treatment. Therefore, caution is recommended in giving aspirin to these patients.

Risk factors predicting thrombotic complications were specifically looked for in a cohort study of 100 consecutive patients with ET diagnosed between 1978 and 1988 and subsequently checked at least every 2 months [26]. The patients received busulphan when the platelet count exceeded $1,000 \times 10^9/L$ and/or when a major thrombotic or haemorrhagic event occurred. Twenty thrombotic episodes (arterial 17, venous 3) were observed (6.6% /patient-year) in the study. When the incidence of thrombosis was analyzed in different age groups, a clear correlation between aging and vascular complications was observed. The rate of thrombosis was also higher

Table 2.

Thrombo-hemorrhagic Risk Stratification in Essential Thrombocythemia.

Low risk	Age <60 years, and No history of thrombosis, and Platelet count < $1,500 \times 10^9/L$
High risk	Age >60 years, or A previous history of thrombosis, or Platelet count $\geq 1,500 \times 10^9/L$

Correction of cardiovascular risk factors (smoking, obesity, hypertension) is recommended in all patients

in those with a previous history of thrombotic events, despite the fact that all these patients were treated with cyto-reductive drugs. These risk factors were confirmed by other investigators [13,21,27,28]. Thrombotic events have been reported to be relatively infrequent below the age of 40 and to have the highest incidence in patients over 60-70 years of age [27]. Aging may also influence the severity of thrombotic complications. In fact, although isolated reports indicate the possibility of life-threatening thromboses in young ET patients [29], the incidence of severe thromboses was only about 1% per year in 56 young thrombocytemic subjects after a mean follow-up of 4.7 years [28]. Most ischemic complications in this group were represented by migraine, headache and erythromelalgia. A prior history of thrombosis was also confirmed to be a significant risk factor for subsequent vascular complications [13,21]. Colombi et al. [21] reported that the prevalence of thrombosis was increased by the presence of a prior thrombotic event from 16 to 57%.

Summing up, a category of ET patients at particularly higher risk of bleeding and thrombosis can be identified, namely those over 60 years old or with a history of a thrombosis or platelet count above $1,500 \times 10^9/L$ (Table 2). Most authorities recommend that myelosuppressive treatment for the thrombocytosis should be focused on these high-risk patients, whereas a different policy should be considered for the remainder [5,30-32].

2. Management of Lower-risk ET Patients

The natural history of untreated, lower-risk ET patients was evaluated in a prospective, controlled study. 65 ET patients with age below 60 years, no history of thrombosis or major bleeding and platelet count below $1,500 \times 10^9/L$ were compared to 65 age and sex matched normal controls. Patients were not treated with cyto-reductive therapy, until the occurrence of major clinical events. After a median follow-up of 4.1 years, the incidence of thrombosis in patients and controls was 1.91 and 1.5% patient-year, respectively. The age and sex adjusted risk rate ratio was 1.43 (95% c.i. 0.37-5.4).

No major bleeding was observed. This study indicate that the thrombotic risk of young, asymptomatic ET patients is not significantly increased compared to the normal population. Another cohort of lower-risk ET patients was followed by Briere and colleagues [33]. This series consisted of 20 asymptomatic cases (median age 40 years, range 7-64 years; median platelet count $909 \times 10^9/L$; range $600-1470 \times 10^9/L$) observed for a median of 6.7 years, without a control group. In 13 patients, treatment with hydroxyurea had to be started because of: a) the onset of major vascular events in four cases (myocardial infarction, surgery of an atheromatous arterial stenosis, aortic aneurysm and portal vein thrombosis); b) minor ischaemic events in three, and c) increased age, increased platelet count or the need for surgery in six patients, even though they were in good health. The other seven patients remained without treatment except for anti-aggregating agents. The rates of major and total thrombotic complications in this cohort were 3 and 5.1%/pt-yr, respectively. It should be stressed that none of the complications observed in these two cohorts was fatal. Thrombotic deaths seem very rare in lower-risk ET subjects and data showing that fatalities can be prevented by starting cytoreductive drugs early have not been produced.

Therefore, one can conclude that withholding chemotherapy might be justifiable in asymptomatic, young ET patients with a platelet count below $1,500 \times 10^9/L$, based on their very low risk of developing fatal thrombotic or bleeding events and for the concern about the potential leukemogenicity of cytotoxic drugs (see below).

Having made this generalization concerning myelosuppressive therapy, it may be rational to propose a primary antithrombotic prophylaxis with aspirin for reducing the rate of vascular complications in these asymptomatic patients [34]. Aspirin has received a wide acknowledgement for efficacy in ET patients with microvascular disturbances, such as erythromelalgia or transient cerebral or ocular ischaemia [14,15]. In the absence of contraindications and/or side effects, a dose of 100-300 mg/day is required in the acute management of these patients. Cyto-reduction usually relieves these symptoms although continued use of aspirin is indicated when a reoccurrence of symptoms is observed with a normal platelet count. The use of aspirin in ET patients at a dose of 75-100 mg/day is also recommended as secondary prophylaxis for major arterial thrombosis [5]. In the absence of clinical trials in the setting of ET, this recommendation is largely based on the assumption that its use is associated with a risk reduction comparable to that achievable in other clinical conditions [35]. However, in prescribing anti-aggregating agents one should consider the risk of bleeding. This is particularly important in ET patients, who may have platelet functional defects [22]. In a recent case-control study in normal subjects the use of enteric-coated or buffered aspirin at average daily doses of 325 mg or less carried a two to three-fold relative increase in the risk of major upper-gastrointestinal hemorrhages [36] indicating that there is increased risk of bleeding even with low-dose

aspirin. However, such bleeding is very rarely associated with irreversible morbidity or mortality.

Pregnancy in asymptomatic ET patients deserve special considerations. ET may jeopardize the outcome of pregnancy. Approximately 50% of pregnancies develop obstetric complications, including recurrent abortion, particularly in the first trimester, premature delivery, fetal growth retardation and abruptio placenta. The likely mechanism of these complications is placental infarction. Thus, some authors recommend the use of aspirin [4] or sub-cutaneous heparin [37] during pregnancy, particularly in those cases who have had previous fetal losses. In a review of the relevant literature, the use of aspirin was associated with a more successful outcome of pregnancy than in those managed without the drug [38]. However, successful pregnancies may also occur in untreated ET women. In a single institutional study from Mayo Clinic of 34 pregnancies occurring in 18 women with ET, Beressi et al. [39] were unable to substantiate the benefit of specific therapy during pregnancy or delivery. Consequently, they do not recommend any prophylactic therapy in asymptomatic pregnant women with ET. In symptomatic patients, α -interferon (see also below) has been used successfully and without relevant side effects [40]. However, only very few anecdotal reports are available and the use of α -interferon in pregnant women with ET needs to be further investigated. At present, a definitive proposal for the most appropriate management strategy for pregnancy in women with ET cannot be given.

3. Management of High-risk ET Patients

Patients aged more than 60 years or with platelet count exceeding $1,500 \times 10^9/L$, or with a previous history of thrombosis or major bleeding are candidates to receive a cytoreductive drug (Table 3).

4. Hydroxyurea

Hydroxyurea (HU) has emerged as the treatment of choice in patients with ET because of its efficacy and

Table 3.

Current Recommendations for Management of Patients with Essential Thrombocythemia.

Low risk	Avoid cytoreductive drugs (reconsider if complications)
	Low-dose aspirin (100-300 mg/die) for microvascular symptoms (e.g. erythromelalgia)
High risk	Cytoreduction
	Hydroxyurea as first choice
	Consider Interferon or Anagrelide in younger patients (< 40 years)
	Consider Busulfan in older patient (>70 years)
	Low-dose aspirin if thrombotic history

only rare acute toxicity [31,33,41]. The drug is given at an initial dose of 15-20 mg/kg/day, with adjustments to maintain reduction of platelet values, ideally to less than $400 \times 10^9/L$ without excessive lowering of the neutrophil count. Continuous treatment with HU has been shown to reduce the platelet count to below $500 \times 10^9/L$ within 8 weeks in 80% of patients. Lowering the platelet count by HU is associated with significant improvement in acute ischaemic or hemorrhagic symptoms. In a randomized clinical trial, the efficacy of HU in preventing thrombosis in ET patients aged >60 years, or with a history of previous thrombosis, or with a platelet count above $1,500 \times 10^9/L$ has been shown [42]. One hundred and fourteen patients (35 males and 79 females, median age 68 years, range 40-85 years; median platelet count $788 \times 10^9/L$, range $533-1240 \times 10^9/L$) were randomized to long-term treatment with HU (n=56) or to no cytoreductive treatment (n=58). During a median follow-up of 27 months, two thromboses (one stroke and one myocardial infarction) were recorded in the HU-treated group (1.6%/pt-yr) compared with 14 (one stroke, five transient ischaemic attacks, five peripheral arterial occlusions, one deep vein thrombosis and two patients with superficial thrombophlebitis) in the control group (10.7% pt-yr; $P=0.003$).

Hematopoietic impairment, leading to neutropenia and macrocytic anaemia, is the major short-term toxic effect of HU. Neutropenia is dose-related and generally quickly reversible if the drug is discontinued for a few days. Unusual side effects of HU include fever and cutaneous symptoms [43]. A recently described complication is painful leg ulcers that are usually difficult to treat and require cessation of the drug [44]. Withdrawal is followed by a rebound of platelet counts. Failure of HU to provide adequate control of the platelet count was reported in 6 out of 29 (21%) patients included in a PVSG protocol [8], and in 9/79 (11%) in a French series [33].

The role of HU in enhancing the risk of leukaemic transformations is one of the major issues currently under discussion in the question of using chemotherapy for ET. HU, being a non-alkylating agent, is generally thought to be non-mutagenic; however, long-term follow-up studies of HU-treated patients with PV and ET revealed that some cases developed acute leukemia [45-48]. These reports cast doubts on the innocence of HU in the process of leukemogenicity. Even when used as a single agent in the treatment of PV and ET, the reported rate of acute leukemia ranges between 3.5 and 10% and this fatal complication is encountered 4-10 years after the start of treatment. Although it is likely that ET patients have an intrinsic likelihood of acute leukaemic transformation, the precise incidence in untreated patients is not known. A review of the literature from 1981 to 1994 [49] identified a total of 40 Ph1-negative ET cases transformed into AL after a mean time from presentation of 6.5 years. Three major factors appear to facilitate blastic transformation: cytogenetic abnormalities [46], myelofibrotic features [8] and the use of other cytotoxic treatments [50]. About 5% of ET

patients have a cytogenetic abnormality, mostly involving chromosomes 1, 2, 5, 17, 20 and 21. The 17p deletion has been recently described in a high proportion of ET patients who developed acute myeloid leukemia and myelodysplasia following treatment with hydroxyurea [48].

When balancing benefits and risks, one can conclude that there is convincing evidence for giving HU to ET patients at higher risk for major thrombotic complications. In contrast, the risk of acute leukemia associated with the use of HU is more difficult to accept in young patients at low-risk for thrombosis. At present, we recommend using HU only for the treatment of high-risk ET patients.

5. Busulphan

Busulphan is an alkylating agent with a specific action on the megakaryocyte proliferation [51]. It should be given in a dose of 2-4 mg daily, according to hematological response, under weekly control of platelet count. After normalization of the platelet count, adequate long-term control of thrombocytosis can be obtained with intermittent courses of the drug, allowing long intervals without the need for therapy. With this schedule, the secondary effects of the drug usually observed at higher doses, such as bone marrow aplasia, skin pigmentation, amenorrhea and pulmonary fibrosis, can be avoided. Alkylating agents, such as chlorambucil, were associated with an excess incidence of malignancies in polycythemia vera [52]. Although busulphan was not found to induce leukemia or other cancers in PV and ET patients [51,53], concerns about leukemogenicity suggest to limit its indication to elderly patients, where the convenience of its use outweigh the potential leukemogenic risk [5,51].

6. Interferon

Recombinant interferon- α (IFN) is an active agent in myeloproliferative disorders with cytoreductive activity that is virtually devoid of mutagenic risk. The rationale for this drug includes its myelosuppressive activity and its ability to antagonize the action of platelet-derived growth-factor (PDGF), a product of megakaryopoiesis which initiates fibroblast proliferation. The precise mechanism of action, however, has not yet been fully elucidated. In ET patients, IFN has been evaluated in several cohort studies [reviewed in 54]. Overall results in a total of 212 patients indicate that reduction of platelet count below $600 \times 10^9/L$ can be obtained in about 90% of cases after about 3 months with an average dose of about 3 million IU daily. Time and degree of the platelet reduction during the induction phase were dose dependent. During maintenance the IFN dose could be tapered, but if IFN is suspended platelet count rebounds in the majority of patients. IFN is not known to be teratogenic and it does not cross the placenta. Thus, it has been used successfully throughout pregnancy in some ET patients with no adverse foetal or maternal outcome.

Side effects are a major problem with this drug [54,55]. Fever and flu-like symptoms are experienced by most patients and usually require contemporaneous administration of paracetamol. Signs of chronic IFN toxicity, such as weakness, myalgia, weight and hair loss, severe depression and gastrointestinal and cardiovascular symptoms, necessitate drug cessation in a relevant proportion of patients. In a recent review of 273 cases published in the literature [54], IFN therapy was terminated in 25% (67 cases) against the primary treatment plan. The rate of withdrawal ranged between zero and 66% between studies. The wide range may be partly explained by the difference in the observation time lasting from one month to 4 years in the reported patients. The most common reasons for withdrawal were IFN-related side effects in 55% and patient refusal in 10%. Thus far, no leukemogenic effects have been observed. Therefore, despite high cost and toxicity, IFN remains a promising agent in cytoreductive treatment of ET, especially in younger patients. Clinical studies comparing IFN to HU or anagrelide (see below) are currently ongoing.

7. Anagrelide

Anagrelide is a member of the imidazo(2,1-b)quinazolin-2-one series of compounds with an inhibitory activity on platelet aggregation in both humans and animals. In addition, it has in humans a species-specific platelet-lowering effect observed at dose levels lower than those required to inhibit platelet aggregation. Because of this, the drug has been tested in patients with clonal thrombocytosis and has been shown to have potent platelet reducing activity [55-57].

The mechanism whereby anagrelide reduces platelet count without affecting the white count or normally the red blood cells is not yet completely understood, but there are data showing that its major action is the inhibition of megakaryocytic maturation. No chromosomal damage has been reported in relation to its use. The efficacy of anagrelide in ET has been assessed in non-comparative clinical studies [58]. Response was defined as a platelet count under 500 or $600 \times 10^9/l$ or a 50% drop in platelet count. A response rate of 60 to 93% was reported, irrespectively of age, sex, spleen size, bleeding time, clinical symptoms or prior treatment. The average dose required to control platelet count was 2 to 2.5 mg per day and, in most cases, the median time for response was 3-4 weeks, although delayed responses of up to 24 months were described. Patients refractory to HU responded to anagrelide in 68% of cases. Continuous therapy is required because the platelet count rebounds in a few days after withdrawal of the drug.

The most serious complications of anagrelide are cardiac, including palpitations or forceful heart beats (27% of patients) tachycardia and other arrhythmias (< 10%) and congestive heart failure (2%) [58]. In addition, the vasodilating effect of the drug is the underlying cause of headache, which is the more frequent side effect (occurring in more than one-third of patients), fluid retention or edema (24% of cases), diz-

zness (15%) and postural hypotension. Gastrointestinal complications (nausea, abdominal pain and diarrhoea) and transient rash have been reported less frequently. Sudden death was observed in two patients given anagrelide: one death was related to a pulmonary infiltrate and the other to congestive heart failure. Overall, 16% of 424 evaluable thrombocytemic patients with MPDs, including 262 with ET, discontinued anagrelide treatment because of side effects. Leukaemic transformation has not been observed for up to 55 months of treatment.

The long-term efficacy and safety of Anagrelide has been recently analyzed in 35 young patients with ET (median age 38 yrs, range 17-48) followed in a single institution for a median follow-up period of 10.8 years (range 7-15.5) [59]. The overall initial response rate was 94% and the reduction of platelet count was maintained in 66% of patients over the study period. Eight patients (24%) experienced a more than 3 g/dL decrease in hemoglobin level and three (9%) discontinued treatment because of toxicity. Most importantly, 7 patients (20%) experienced a total of 10 thrombotic episodes, while on therapy, and a similar proportion experienced major bleeding complications. This study suggested that the thrombohemorrhagic complications might have been due to less than optimal platelet cytoreduction with the anagrelide doses used. None of the patients developed acute leukemia. Thus, long-term therapy with anagrelide appears to be relatively well-tolerated but thrombohemorrhagic complications continue to occur. The final place of this drug in the therapeutic strategy of ET patients remains to be established in controlled clinical trials, such as the PT1 trial currently ongoing in the U.K.

References

1. Fialkow PJ, Faguet GB, Jacobson RJ, et al. Evidence that essential thrombocythemia is a clonal disorder with origin in a multipotent cell. *Blood*. 1981;58:916-919.
2. Harrison CN, Gale RE, Machin SJ, Linch DC. A large proportion of patients with a diagnosis of essential thrombocythemia do not have a clonal disorders and may be at lower risk of thrombotic complications. *Blood*. 1999;93:417-424.
3. Murphy S. Therapeutic dilemmas: balancing the risk of bleeding, thrombosis, and leukemic transformation in myeloproliferative disorders (MPD). *Thromb Haemostas*. 1997;78:622-626.
4. Murphy S, Iland HJ. Thrombocytosis. In: *Thrombosis and Hemorrhage* (1st ed.) Loscalzo J and Schafer AL eds. Williams and Wilkins, Baltimore, 1994. pp. 597-612.
5. Pearson TC. Primary Thrombocythaemia: diagnosis and management. *Br J Haematol*. 1991;78:145-148.
6. Rozman C, Giral M, Feliu E, et al. Life expectancy of patients with chronic nonleukemic myeloproliferative disorders. *Cancer*. 1991;67:2658-2663.
7. Murphy S, Iland HJ, Rosenthal D, et al. Essential thrombocythemia: an interim report from the Polycythemia Vera Study Group. *Semin Hematol*. 1986;23:177-182.
8. 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.
9. Dudley JM, Messinezy M, Eridani S, et al. Primary thrombo-

- cythemia: diagnostic criteria and a simple scoring system for positive diagnosis. *Br J Haematol.* 1989;71:331-335.
10. Kutti J, Wadenvik H. Diagnostic and differential criteria of essential thrombocythemia and reactive thrombocytosis. *Leuk Lymphoma.* 1996;22:41-45.
 11. Sawyer BM, Westwood NB, Pearson TC. Circulating megakaryocyte progenitor cells in patients with primary thrombocythemia and reactive thrombocytosis: results using a serum-deprived culture assay and positive detection technique. *Eur J Hematol.* 1994;53:108-113.
 12. Lengfelder E, Hochhaus A, Kronawitter U, et al. Should a platelet limit of 600 x 10⁹/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.
 13. Landolfi R, Rocca B, Patrono C. Bleeding and thrombosis in myeloproliferative disorders: mechanisms and treatment. *Crit Review Oncol Hematol.* 1995;20:203-222.
 14. Koudstaal PJ, Koudstaal A. Neurologic and visual symptoms in essential thrombocythemia: efficacy of low-dose aspirin. *Semin Thromb Haemostas.* 1997;23:365-370.
 15. Van Genderen PJJ, Michiels JJ. Erythromelalgia: a pathognomonic microvascular thrombotic complication in essential thrombocythemia and polycythemia vera. *Semin Thromb Haemostas.* 1997;23:357-364.
 16. De Stefano V, Teofili L, Leone G, et al. Spontaneous erythroid colony formation as the clue to an underlying myeloproliferative disorder in patients with Budd-Chiari syndrome or portal vein thrombosis. *Semin Thromb Haemostas.* 1997;23:411-418.
 17. Barbui T, Cortelazzo S, Viero P, et al. Thrombohaemorrhagic complications in 101 cases of myeloproliferative disorders: Relationship to platelet number and function. *Eur J Cancer Clin Oncol.* 1983;19:1593-1599.
 18. Bellucci S, Janvier M, Tobelem G, et al. Essential thrombocythemia: Clinical evolutionary and biological data. *Cancer.* 1986;58:2440-2447.
 19. Hehlmann R, Jahn M, Baumann B, et al. Essential thrombocythemia: Clinical characteristics and course of 61 cases. *Cancer.* 1988;61:2487-2496.
 20. Fenaux P, Simon M, Caulier MT, et al. Clinical course of essential thrombocythemia in 147 cases. *Cancer.* 1990;66:549-556.
 21. Colombi M, Radaelli F, Zocchi L, et al. Thrombotic and hemorrhagic complications in essential thrombocythemia. *Cancer.* 1991;67:29269-2930.
 22. Finazzi G, Budde U, Michiels JJ. Bleeding time and platelet function in essential thrombocythemia and other myeloproliferative syndromes. *Leuk Lymphoma.* 1996;22(suppl 1):71-78.
 23. Rinder HM, Schuster JE, Rinder CS, et al. Correlation of thrombosis with increased platelet turnover in thrombocytosis. *Blood.* 1998;91:1288-1293.
 24. Budde U, Scharf RE, Franke P, et al. Elevated platelet count as a cause of abnormal von Willebrand factor multimer distribution in plasma. *Blood.* 1993;82:1749-1757.
 25. Van Genderen PJJ, Michiels JJ, van der Poel-van de Luytgaarde SCPAM, et al. Acquired von Willebrand disease as a cause of recurrent mucocutaneous bleeding in primary thrombocythemia: relationship with platelet count. *Ann Hematol.* 1994;69:81-84.
 26. 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.
 27. Randi ML, Fabris F, Rossi C, et al. Sex and age as prognostic factors in essential thrombocythemia. *Haematologica.* 1992;77:402-404.
 28. McIntyre K, Hoagland H, Silverstein M, et al. Essential thrombocythemia in young adults. *Mayo Clin Proc.* 1991;66:149-154.
 29. Mitus AJ, Barbui T, Shulman LN, et al. Hemostatic complications in young patients with essential thrombocythemia. *Am J Med.* 1990;88:371-375.
 30. Kutti J. The management of thrombocytosis. *Eur J Haematol.* 1990;44:81-88.
 31. Schafer AI. Essential thrombocythemia. *Progr Hemostas Thromb.* 1991;10:69-96.
 32. Tefferi A, Silverstein MN, Hoagland HC. Primary thrombocythemia. *Semin Oncol.* 1995;22:334-340.
 33. Barbui T, Finazzi G, Dupuy E, et al. Treatment strategies in essential thrombocythemia. *Leuk Lymphoma.* 1996;22(suppl 1):149-160.
 34. Griesshammer M, Bangerter M, vanVliet HHD, et al. Aspirin in essential thrombocythemia: status quo and quo vadis. *Semin Thromb Haemostas.* 1997;23:371-378.
 35. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J.* 1994;308:81-106.
 36. Kelly JP, Kaufman DW, Jurgelson JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet.* 1996;348:1413-1416.
 37. Pagliaro P, Arrigoni L, Muggiasca ML, et al. Primary thrombocythemia and pregnancy. Treatment and outcome in fifteen cases. *Am J Hematol.* 1996;53:6-10.
 38. Griesshammer M, Heimpel H, Pearson TC. Essential thrombocythemia and pregnancy. *Leuk Lymphoma.* 1996;22(suppl 1):57-63.
 39. Beressi AH, Tefferi A, Silverstein MN, et al. Outcome analysis of 34 pregnancies in women with essential thrombocythemia. *Arch Intern Med.* 1995;155:1217-1222.
 40. Shpilberg O, Shimon I, Sofer O, et al. Transient normal platelet count and decreased requirement for interferon during pregnancy in essential thrombocythemia. *Br J Haematol.* 1996;92:491-493.
 41. Lofvenberg E, Walhlin A. Management of polycythemia vera, essential thrombocythemia and myelofibrosis with hydroxyurea. *Eur J Haematol.* 1988;41:375-381.
 42. 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.
 43. Daoud MS, Gibson LE, Pittelkow MR. Hydroxyurea dermatopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol.* 1997;36:178-182.
 44. Best P, Daoud MS, Pittelkow MR et al. Hydroxyurea-induced leg ulceration in 14 patients. *Ann Intern Med.* 1998;128:29-32.
 45. Nand S, Stock W, Godwin J, et al. Leukemogenic risk of hydroxyurea therapy in polycythemia vera, essential thrombocythemia and myeloid metaplasia with myelofibrosis. *Am J Hematol.* 1996;52:42-46.
 46. Lfvenberg 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.
 47. Weinfield A, Swolin B, Westin J. Acute leukaemia after hydroxyurea therapy in polycythemia vera and allied disorders: prospective study of efficacy and leukaemogenicity with therapeutic implications. *Eur J Haematol.* 1994;52:134-139.
 48. Sterkers Y, Preudhomme C, Lai J-L, et al. Acute myeloid leukemia and myelodysplastic syndromes following essential thrombocythemia treated with hydroxyurea: high proportion of cases with 17p deletion. *Blood.* 1988;91:616-622.
 49. Shibata K, Shimamoto Y, Suga K, et al. Essential Thrombocythemia terminating in acute leukemia with minimal myeloid differentiation. A brief review of recent literature. *Acta Haematol.* 1994;91:84-88.

50. Finazzi G, Ruggeri M, Rodeghiero F, Barbui T. Second malignancies in patients with essential thrombocythaemia treated with busulfan and hydroxyurea: long-term follow-up of a randomized clinical trial. *Br J Haematol.* 2000;110:577-583.
51. Van de Pette JEW, Prochazka AV, Pearson TC, et al. Primary thrombocythemia treated with busulfan. *Br J Haematol.* 1986; 62:229-237.
52. Berk P, Goldberg J, Donovan P, et al. Therapeutic recommendations in polycythemia vera based on polycythemia vera study group protocols. *Semin Hematol.* 1986;23:132-143.
53. Haanen C, Mathe G for the EORTC. Treatment of polycythemia vera by radioactive phosphorus or busulphan. *Br J Cancer.* 1981;44:75-78.
54. Lengfelder E, Griesshammer M, Hehlmann R. Interferon-alpha in the treatment of essential thrombocythemia. *Leuk Lymphoma.* 1996;22(suppl 1):135-142.
55. Tefferi A, Elliot MA, Solberg LA Jr, et al. New drugs in essential thrombocythemia and polycythemia vera. *Blood Reviews.* 1997;11:1-7.
56. Tefferi A, Silverstein MN, Pettitt RM, et al. Anagrelide as a new platelet-lowering agent in essential thrombocythemia: mechanism of action, efficacy, toxicity, current indication. *Semin Thromb Hemostas.* 1997;23:379-384.
57. Pettitt RM, Silverstein MN, Petrone ME. Anagrelide for control of thrombocythemia in polycythemia and other myeloproliferative disorders. *Semin Hematol.* 1997;34:51-54.
58. Anagrelide Study Group. Anagrelide, a therapy for thrombocytopenic states: experience in 577 patients. *Am J Med.* 1992; 92:69-76.
59. Storen EC, Tefferi A. Long-term use of anagrelide in young patients with essential thrombocythemia. *Blood.* 2001;97:863-866.