

# EDUCATION SESSION 8: MYELOPROLIFERATIVE DISEASES



## Essential Thrombocythemia

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### Introduction

Classification of the chronic myeloid disorders (CMD) is based on certain molecular, cytogenetic, morphologic, and clinical characteristics<sup>(1)</sup>. In the context of a CMD, the demonstration of the *bcr/abl* genetic translocation between chromosomes 9 and 22 mandates a diagnosis of chronic myelocytic leukemia (CML). In the absence of t(9;22), a clonal increase in red cell mass (RCM) defines polycythemia vera (PV). Accurate diagnosis is not always easy in the remaining subgroups of CMD. In general, the presence of dyserythropoiesis and peripheral pancytopenia is consistent with the diagnosis of the myelodysplastic syndrome (MDS). The presence of bone marrow fibrosis that is not associated with either CML or MDS suggests the diagnosis of myelofibrosis with myeloid metaplasia (MMM). Finally, essential thrombocythemia (ET) represents a chronic state of thrombocytosis that is neither reactive nor associated with MDS, CML, MMM, or PV.

### Pathogenesis

Clonal studies based on X chromosome-associated genes or their products have consistently shown a stem cell origin for the clonal process in both MDS and chronic myeloproliferative disorders (CMPD)<sup>(2-7)</sup>. It is generally believed that

the primary clonogenic event governs disease expression (8). Alternatively, clonal generation at either hierarchically different stem cell levels may underlie the phenotypic diversity among the CMPDs<sup>(9)</sup>. However, lineage heterogeneity may also occur within a particular disease group,<sup>(7,10,11)</sup> and its biological implication is further confounded by the recent demonstration of polyclonal hematopoiesis in ET<sup>(7)</sup> and monoclonal hematopoiesis in normal elderly females<sup>(12)</sup>. Recent studies have focused on pathogenetic mechanisms responsible for the thrombocytosis in ET.

In general, serum thrombopoietin (TPO) levels are inversely correlated with platelet and megakaryocyte mass<sup>(13)</sup>. In patients with ET, however, serum TPO levels are usually elevated or normal despite an increased megakaryocyte mass<sup>(14-16)</sup>. The discrepancy has been attributed to ineffective TPO clearance because of markedly reduced TPO-receptor (c-Mpl) expression in platelets and megakaryocytes, rather than a systemic overproduction of TPO<sup>(17,18)</sup>. Similarly, recent studies in ET have not revealed structural mutations of c-Mpl,<sup>(19)</sup> and decreased c-Mpl expression is not specific to ET and is also seen in MMM and PV<sup>(20)</sup>.

### Diagnosis

During evaluation of thrombocytosis, both reactive and a variety of clonal causes need to be entertained (**Table 1**). A persistent and otherwise unexplained elevation in platelet count, in a non-splenectomized patient with normal serum ferritin and C-reactive protein levels, suggests clonal thrombocytosis<sup>(21)</sup>. A bone marrow examination with cytogenetic studies helps exclude the possibility of MDS, AMM, and CML<sup>(22-25)</sup>.

### Clinical aspects

Population-based epidemiologic studies suggest that ET may be the most frequent among the CMPD with an estimated incidence of 2.5/100,000<sup>(26)</sup>. Median age at diagnosis is approximately 60 years and there is a slight preponderance of females<sup>(27)</sup>. Approximately 25% of patients with ET are asymptomatic at presentation. The rest may present with vasomotor symptoms (headaches, transient neurologic or ocular symptoms, distal paraesthesias, and erythromelalgia),

Table 1. Causes of thrombocytosis.

#### 1. Non-clonal

- Iron deficiency
- Splenectomy
- Hemolysis or bleeding
- Infection or inflammation (connective tissue disease, vasculitis)
- Tissue damage (surgery, myocardial infarction, pancreatitis, trauma)
- Malignancy

#### 2. Clonal

- Essential thrombocythemia
- Polycythemia vera
- Agnogenic myeloid metaplasia
- Chronic myelogenous leukemia
- Myelodysplastic syndrome

thrombosis, or bleeding. Thrombotic events include strokes, transient ischemic attacks, retinal artery or venous occlusions, coronary artery ischemia, pulmonary embolism, hepatic or portal vein thrombosis, deep vein thrombosis, and digital ischemia. The incidence of thrombotic events, before and after diagnosis, are 15 and 11%, respectively<sup>(28)</sup>. Bleeding complications are both less frequent and less serious and have been significantly associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Leukemic conversions occur in less than 5% of all patients with ET<sup>(27)</sup>. Treatment with certain agents may increase the risk of acute leukemia<sup>(29,30)</sup>. In contrast, specific therapy may or may not modify the risk of fibrotic transformation that occurs in less than 5% of patients with ET. Spontaneous early-term abortions occur in up to 45% of the pregnancies in ET<sup>(31)</sup>.

### Prognostic Factors

Age and a history of previous thrombosis are the most powerful predictors of recurrent thrombosis in ET<sup>(32)</sup>. The ratio of thrombotic events to the total number of person-years of observation was 1.7 for patients younger than age 40 years, 15.1 for those older than 60 years, and 31.4 for those with a previous history of thrombosis. Neither the degree of thrombocytosis nor the presence of platelet function abnormalities has been correlated with thrombotic risk in ET<sup>(33)</sup>. The role of cardiovascular risk factors in the occurrence of thrombosis is disputed<sup>(34)</sup>. Based on these risk factors, patients with ET may be categorized into different risk groups with different treatment strategies (**Table 2**).

### Treatment

The most frequent symptoms in ET are vasomotor and are easily managed with low-dose ASA (75-100 mg/day)<sup>(35)</sup>. Bleeding complications are less frequent and may be prevented by the avoidance of NSAIDs<sup>(36)</sup>. On the other hand, approximately 20% of the patients present with major thrombotic events and another 15% may experience recurrent thrombosis<sup>(27,32)</sup>. Therefore, the primary objective in the management of ET is to reduce the risk of thrombosis.

In a randomized study, the use of HU, compared to no treatment, has been shown to reduce the risk of thrombosis, in high-risk patients (**Table 2**), from 24% to less than 4%<sup>(37)</sup>. Therefore, current evidence supports the use of HU in high-risk patients with ET. Furthermore, maintenance of the platelet count under 400,000/micL may be associated with further reduction in thrombotic risk<sup>(27,38)</sup>.

Thrombotic events in low-risk patients with ET are too infrequent to justify the long-term use of potentially harmful agents<sup>(32)</sup>. The risk may be higher, however, in the presence of cardiovascular risk factors and/or extreme uncontrolled thrombocytosis<sup>(32,34,39)</sup>. Whether drug therapy is indicated in this particular situation remains controversial.

To date, there is no randomized study that directly implicates HU as being more leukemogenic than any other therapeutic strategy, either in ET. On the other hand, there are several non-randomized studies that have either sup-

ported or refuted a significant increase in leukemic conversion associated with the long-term use of HU. Reported incidence rates of leukemic conversion, when HU is used alone, range from 0-5% in ET<sup>(29,30,40,41)</sup>. However, several studies have suggested a further increase in leukemia risk when HU is combined with other agents<sup>(29,30)</sup>. Furthermore, a recent study revealed a high frequency of 17p deletions in acutely transformed patients with ET treated with HU, suggesting a potential association<sup>(30)</sup>. Regardless, the observed excess risk may be related to disease biology rather than drug effect.

### Alternative Platelet-Lowering Agents in ET

Anagrelide is an oral imidazoquinazoline derivative that has a species-specific platelet lowering effect in humans (**Table 3**)<sup>(42)</sup>. The platelet inhibitory activity of anagrelide is seen only at higher than therapeutic doses used for controlling thrombocytosis and should not be a concern during the treatment of patients with ET<sup>(43)</sup>. We have previously shown that the mechanism of action may be related to interference with megakaryocyte maturation<sup>(44)</sup>. Anagrelide is capable of reducing the platelet count, to less than 600,000/micL, in more than 80% of previously treated and untreated patients with ET and related diseases<sup>(45)</sup>. Initial adult dose is 0.5 mg four times-a-day. Side effects and contraindications in the use of anagrelide are outlined in **Table 4**. Nonischemic cardiomyopathy occurs rarely and the drug should be used carefully, if at all, in patients with heart disease.

Alpha interferon controls the thrombocytosis associated with any myeloproliferative disorder including ET<sup>(46)</sup>. An overview of the reported literature indicates an 86% hematologic response rate associated with a 32% rate of reduction in spleen size (dose ranges of 3 to 5 million SC daily)<sup>(46,47)</sup>. Long-term therapy is feasible and may be associated with lower maintenance doses or unmaintained remissions<sup>(48-51)</sup>. However, despite significant reduction in megakaryocyte mass, clonal hematopoiesis persists and alpha interferon is not curative<sup>(52)</sup>. Current evidence does not support choosing alpha interferon over HU or anagrelide in the treatment of high-risk patients with ET. Furthermore, the drug is more expensive and less tolerable. As such, we have restricted the use of alpha interferon, in ET, to high-risk women of childbearing age and to those who are pregnant.

Table 2. Thrombosis-directed risk stratification in essential thrombocythemia.

	Age > 60 years and/or history of thrombosis	Cardiovascular risk factors and/or extreme thrombocytosis*
<b>Low-risk</b>	No	No
<b>Intermediate-risk</b>	No	Yes
<b>High-risk</b>	Yes	Yes or No

\* Platelet count greater than 1.5 million/mL.

Table 3. Clinical properties of hydroxyurea and anagrelide.

	Hydroxyurea	Anagrelide
<b>Drug class</b>	antimetabolite	Imidazoquinazolin
<b>Mechanism of action</b>	Not genotoxic, impairs DNA repair by inhibiting ribonucleotide reductase	Interferes with terminal differentiation of megakaryocytes
<b>Specificity</b>	Affects all cell lines	Affects platelet production only
<b>Pharmacology</b>	Half-life @ 4 hours, renal excretion	Half-life @ 1.5 hours, renal excretion
<b>Starting dose</b>	500 mg PO BID or TID	0.5 mg PO TID or QID
<b>Onset of action</b>	@ 3-5 days	@ 1-2 weeks
<b>Side-effects observed in &gt; 10% of patients</b>	Neutropenia, anemia, oral ulcers, hyperpigmentation, rash, nail changes	Headache, forceful heart beats, palpitations, diarrhea, fluid retention
<b>Side effects observed in &lt;10% of patients</b>	leg ulcers, lichen planus-like lesions of the mouth and skin, nausea, diarrhea, fever, liver function test abnormalities	Congestive heart failure, arrhythmias, anemia, light headedness, nausea
<b>Contraindications</b>	Neutropenia, pregnancy, childbearing potential.	Congestive heart failure, pregnancy, childbearing potential.

Pipobroman is an oral piperazine derivative (1,4-bis(3-bromopropionyl)-piperazine) structurally classified as an alkylating agent<sup>(53)</sup>. The drug is not available in the United States and is used widely in Europe for the treatment of PV and ET. Initial dose is 1 mg/kg/day and anticipated side effects include nausea, abdominal cramps, diarrhea, stomatitis, and dry skin. The general impression, in the use of pipobroman in ET, is that it is as effective as HU and less leukemogenic than chlorambucil or <sup>32</sup>P.

Thromboxane biosynthesis is elevated in both ET and PV, and the in vivo activity is suppressible with low-dose ASA (50 mg/day)<sup>(54,55)</sup>. These observations suggested that low-dose ASA may be safe and possibly effective in preventing thrombosis in ET and PV<sup>(56,57)</sup>. Subsequently, a recent randomized study demonstrated no increased bleeding associated with the use of low-dose ASA (40 mg/day) despite a laboratory evidence of effective platelet cyclooxygenase inhibition<sup>(56)</sup>. Whether low-dose ASA is effective in reducing the incidence of recurrent thrombosis in PV is currently being investigated<sup>(58)</sup>. In the mean time, we use low-dose ASA (75-100 mg/day) to control vasomotor symptoms and for other clinical indications, in the absence of a bleeding diathesis including a disease-related acquired defect in the von Willebrand protein<sup>(59)</sup>.

#### Management of ET During Pregnancy

We have previously published our experience with 34 pregnancies occurring in 18 patients with ET<sup>(31)</sup>. In that particular study, 45% of the pregnancies ended in spontaneous abortions, primarily occurring in the first trimester. There were no other significant events and all deliveries were uncomplicated. The outcome of pregnancy was not different between patients who received no specific therapy and those treated with ASA alone. Furthermore, three pregnancies were carried to term and resulted in deliveries of healthy babies, despite the use of <sup>32</sup>P or busulfan around the time of

conception. The occurrence of abortions could not be predicted from the disease course, platelet count, or specific therapy. Complications during delivery were infrequent even in the absence of prophylactic platelet apheresis. Therefore, it can not, currently, be concluded that specific therapy influences pregnancy outcome in ET. As such, we currently do not use platelet-lowering agents in low-risk patients with ET. In case of recurrent abortions, the use of low-dose ASA or alpha-interferon is reasonable but of unproven benefit. In high-risk (for thrombosis) women we currently favor the use of alpha interferon<sup>(60-62)</sup>.

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