



Diagnosis of essential thrombocythemia at platelet counts between 400 and 600×10⁹/L

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ABSTRACT

Background and Objectives. Diagnostic criteria for essential thrombocythemia (ET) remain essentially negative, that is, exclusion of other myeloproliferative diseases and causes of reactive thrombocytosis. A platelet count above 600×10⁹/L is still generally considered an absolute diagnostic criterion although new protocols for positive diagnostic criteria have recently been proposed, reducing the stringency of a definite platelet limit. This study demonstrates that a platelet count ≤600×10⁹/L is not a reliable diagnostic criterion for ET, especially in the early stages.

Design and Methods. An ongoing retrospective study by the GIMMC analyzed 2,316 ET patients diagnosed between 1986 and 1995. Of these 2,316 patients, diagnosed according to the PVSG criteria, 68 had a platelet count ≤600×10⁹/L and were analyzed separately; 37 out of 68 were excluded from this analysis because of a follow-up shorter than 2 years and/or because of treatment with myelosuppressive agents. The remaining 31 patients were the subjects of our study.

Results. After a median follow-up of 4.56 years (range 2-9.6 years) none of the 31 patients had a spontaneous decrease of platelets to the normal range. Transformation to a different chronic myeloproliferative disorders was never observed and no patient developed a condition known to produce reactive thrombocytosis. During follow-up, 23 patients (74%) were treated with anti-aggregating drugs, mainly aspirin. The disease did not evolve into acute leukemia in any patient, 1 had a thrombotic event and none presented hemorrhagic episodes. Median platelet count during follow-up was 534×10⁹/L (range 398-997×10⁹/L).

Interpretation and Conclusions. Long term follow-up has documented that our 31 patients were correctly diagnosed as having ET, although platelet count was ≤600×10⁹/L. Our patients were probably in an early phase of their disease and following updated PVSG

criteria would have been misdiagnosed leading to incomplete recognition of the natural history of the disease. Further, because an early diagnosis could also have a clinical relevance, our results outline the need for new criteria for the diagnosis of ET. The exclusion of patients with a platelet count between 400 and 600×10⁹/L may prevent patients, nevertheless at risk of vascular complications, from being treated.

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Key words: essential thrombocythemia, myeloproliferative disorders, reactive thrombocytosis, diagnostic criteria, platelet count, retrospective study

Dameshek was the first, in 1951, to group together chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis with myeloid metaplasia (MMM), under the common heading of chronic myeloproliferative disorders (CMD).¹

More recently and according to current morphologic, biochemical and cytogenetic criteria, clear and concise definitions of CMD have been reviewed.² Philadelphia chromosome-positive (Ph+) ET and CML are distinct malignant disease entities, whereas Ph- ET, PV, and chronic megakaryocytic granulocytic metaplasia (CMGM) or idiopathic myelofibrosis (IM) form a syndrome of related CMD. ET is a clonal disorder characterized in the bone marrow by pathologic expansion of megakaryocytic elements, with a persistent increase in the platelet count.

The diagnostic criteria for ET proposed by the *Polycythemia Vera Study Group* (PVSG) in 1975 were a platelet count above 1,000×10⁹/L and a bone marrow showing megakaryocytic hyperplasia and abundant platelet clumps in the absence of PV, significant myelofibrosis and myelodysplasia.^{3,4} The criterion of a platelet count exceeding 1,000×10⁹/L was mainly directed at the exclusion of reactive thrombocytosis and of other myeloproliferative disorders associated with thrombocytosis, reflecting the reluctance of PVSG clinicians to treat patients considered at low risk of vascular disease.

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However, this criterion resulted in the exclusion of several ET patients with a lesser degree of thrombocytosis. Thus, in 1986 the PVSG modified the minimum platelet count for the diagnosis of ET to $600 \times 10^9/L$.⁵

In the late 1990s^{6,7} the PVSG further updated the criteria previously proposed and changed some requirements, but a platelet count above $600 \times 10^9/L$ was still considered an essential criterion. Furthermore, ET remains a diagnosis of exclusion, and a platelet count above $600 \times 10^9/L$ is still generally considered an absolute diagnostic criterion, although positive criteria have been proposed.⁸⁻²⁰ Here we report on 31 patients, who at diagnosis fulfilled all the updated PVSG criteria except that of the platelet count. Long term follow-up has documented that they were correctly diagnosed as having ET, although their platelet counts were between 400 and $600 \times 10^9/L$.

Design and Methods

Patients

An ongoing retrospective study of the *Gruppo Italiano Malattie Mieloproliferative Croniche* (GIMMC) analyzed 2,316 patients diagnosed as having ET between 1976 and 1996 in 58 Italian hematologic institutions. The aim of the study was to evaluate epidemiologic, prognostic and clinical aspects of ET. An interim report was presented in late 1997.²¹ Patients not fulfilling all PVSG criteria were excluded from subsequent studies or analyzed separately.

Diagnostic criteria

The most frequent requirements for ET diagnosis are the PVSG updated criteria⁵ (Table 1).

Since the diagnosis of ET according to the PVSG criteria is one of exclusion, attempts have been made to formulate positive criteria for distinguishing ET patients from patients with reactive thrombocytoses or other CMD.⁸⁻²⁰ The Rotterdam criteria¹⁷ for the diagnosis of ET are reported in Table 2.

For the purpose of this study we used the PVSG criteria. Of 2,316 patients who entered the retrospective study, 68 patients fulfilled all PVSG updated criteria, but had a platelet count below $600 \times 10^9/L$. We adopted two other requirements to exclude patients with reactive thrombocytosis and patients with different CMD, mimicking ET at diagnosis. Thus we excluded patients treated with myelosuppressive agents and patients with a follow-up shorter than two years.

Although absence of myelosuppressive treatment and follow-up longer than two years are not universally accepted as diagnostic criteria, we arbitrarily considered fulfilling these additional conditions sufficient to exclude patients with reactive thrombocytosis or another CMD.

Study group

Applying these strict criteria, only 31 of 68 patients remained in the study. They had a median age of 49 years (range 16-74 years) and 22 were female (70%). At diagnosis their median platelet count was $512 \times 10^9/L$ (range 394-600). The clinical characteristics of the 31 patients analyzed in this study are reported in Table 3.

Table 1. Updated diagnostic criteria for essential thrombocythemia.

I	Platelet count $> 600 \times 10^9/L$
II	Hematocrit > 40 , 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 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

Table 2. The Rotterdam criteria for the diagnosis of ET proposed by the Thrombocythemia Vera Study Group (TVSG).

Diagnostic and confirmative criteria

A	Diagnostic criteria
A1	Platelet count in excess of $400 \times 10^9/L$ and no known cause of reactive thrombocytosis
A2	Increase and clustering of enlarged and mature megakaryocytes with hyperploid nuclei in bone marrow biopsy material
B	Confirmative criteria
B1	Normal or elevated leukocyte alkaline phosphatase score, normal ESR, and no fever or infection
B2	Normal or increased cellularity of the bone marrow with or without the presence of reticulin fibers in biopsy material
B3	Splenomegaly on palpation, isotope or ultrasound scan, or computer tomogram
B4	Spontaneous erythroid colony formation (EEC) and/or spontaneous megakaryocyte colony formation (CFU-Meg)

Results

The median follow-up was 4.56 years (range 2-9.1 years). During this period, none of the 31 patients had a spontaneous, stable decrease of platelet count to within the normal range and no patients developed a condition known to induce reactive thrombocytosis. Furthermore, transformation from ET to a different CMD was never observed. Thus, these patients have to be considered as having ET. During follow-up 23 out of 31 patients were treated with anti-aggregating drugs (mainly aspirin at a dose of 100 mg/day). No patients developed hemorrhages and only one had a thrombotic event. Platelet count during follow-up is reported in Table 4. After a follow-up of 5 years, 36% of patients had a platelet count $> 600 \times 10^9/L$.

Table 3. Clinical characteristics at diagnosis of the 31 patients with platelet count below $600 \times 10^9/L$ not treated with myelosuppressive therapy and with follow-up exceeding two years.

Sex (male /female) (%)	30/70
Age median (years) (range)	49.3 (16-74)
Platelets ($\times 10^9/L$) mean \pm SD	512 \pm 41.2
Leukocytes ($\times 10^9/L$) mean \pm SD	8 \pm 2.0
Hemoglobin (g/dL) mean \pm SD	13.8 \pm 0.9
Splenomegaly (%)	13
Hepatomegaly (%)	16
Symptomatic patients (%)	13
Bone marrow investigations not evaluable (%)	22.6
reticulon content increased (%)	22.6
Follow-up median (years) (range)	4.56 (2-10)
Platelet value ($\times 10^9/L$) during follow-up (median)	534 (398-997)

Discussion

The diagnosis of ET has been largely based on negative criteria, such as the exclusion of other CMD and secondary thrombocytoses. The updated PVSG criteria^{6,7} still considers a platelet count above $600 \times 10^9/L$ as an absolute requirement for a diagnosis of ET.

Several investigators have proposed laboratory measurements such as platelet size and contents, spontaneous growth of erythroid or megakaryocytic colonies *in vitro*, splenic size, histopathology findings and clonality studies in female patients in an attempt to find positive diagnostic criteria.⁸⁻²⁰ Evidence of platelet-dependent and aspirin-responsive microcirculatory disturbances is considered pathognomonic of ET by one author.²² The same author recently reported on 12 patients with erythromelalgic thrombotic thrombocytopenia presenting at diagnosis with platelet counts between 400 and $600 \times 10^9/L$.²³ Some of these parameters have been included in new protocols for revised diagnostic criteria of ET.^{8,12,17} Following these proposals, the stringency of the platelet limit could be reduced if bone marrow features,²⁴ particularly the increase of megakaryopoiesis, were included in diagnostic criteria of ET.¹⁸ However, to date these new positive criteria proposals are not universally accepted and ET diagnosis is largely considered a diagnosis of exclusion and a platelet count greater than $600 \times 10^9/L$ is still generally recognized as an essential requirement. In our study, we have demonstrated that patients with a platelet count between 400 and $600 \times 10^9/L$ can be diagnosed as having ET with subsequent follow-up confirming the diagnosis. Thus, we think that a definite platelet limit is not a reliable diagnostic criterion for ET. Such selectivity (platelets $>600 \times 10^9/L$) could be accept-

Table 4. Platelet count during the follow-up of the patients in our study.

Follow-up (years)	Number of evaluable patients						
	by years		by PLT counts ($\times 10^9/L$)				
	<400	400	500	600	700	800	900
	499	599	699	799	899	999	
1	31	1	7	17	5	1	
2	31	1	9	15	5	1	
3	17	1	4	8	2	1	1
4	16		5	7	2	2	
5	11	1	1	5	1	3	
6	9		3	1	2	3	
7	3		2		1		
8	3	1	1			1	
9	1				1		
10	1						1

able for therapeutic studies. However, the exclusion of cases with moderate thrombocytosis, probably in early stages of their disease, may lead to incomplete recognition of the natural course of ET and may prevent patients, nevertheless at risk of vascular complications, from being treated.

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All the authors were involved in the conception and design of the study, in the clinical assessment of the patients, collection and interpretation of the data, and gave their final approval of the manuscript. SS and GV wrote the paper. The order in which the names of the authors appear takes into account their contribution to the study.

Disclosures

Conflict of interest: none.

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Manuscript processing

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Potential Implications for clinical practice

- ◆ The current PVSC criteria exclude some patients who do have essential thrombocythemia.
- ◆ This study helps the clinician to make an early and correct diagnosis of this condition.

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