Prevention of thrombosis in polycythemia vera and essential thrombocythemia

Raffaele Landolfi[1,2] **and Leonardo Di Gennaro**[1]

[1]Institute of Internal Medicine and Geriatrics, Haemostasis Research Center; [2]Research Institute Oasi Maria Santissima, Troina; Catholic University School of Medicine, Rome, Italy. E-mail rlandolfi@rm.unicatt.it. *doi: 10.3324/haematol.12604*

Identifying the most safe and effective strategy for reducing the vascular risk of subjects with polycythemia vera and essential thrombocythemia has always been challenging. The mechanisms underlying the thrombotic diathesis of these patients are still largely elusive and, more importantly, the number of large scale studies performed in this specific setting is very limited. Thus, physicians have to rely on approximate and largely subjective estimations of the vascular risk and on consensus-based recommendations. Not surprisingly, the use of several agents is quite heterogeneous among different countries. The European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP), which was established to test the efficacy and safety of low-dose aspirin in polycythemia vera, involved 12 European countries.[1] The participating centers, although with moderate differences among centers and countries, prescribed hydroxyurea and aspirin to a much higher percentage of their patients than that reported in a survey on polycythemia vera treatments performed in the same years among North American centers.[2] After the ECLAP trial, the recommendations on the use of aspirin in polycythemia vera will likely become more uniform but debates on hydroxyurea will probably continue for a long time. In fact, a clinical trial comparing the long-term efficacy and safety of this agent with that of alternative cytoreductive strategies would be very difficult to organize. In this scenario, the large retrospective analysis by De Stefano *et al.* on polycythemia vera and essential thrombocythemia patients with a history of thrombosis, published in this issue of the journal,[3] provides an update of the unmet needs and helps to focus the priorities for future research.

Should we consider polycythemia vera and essential thrombocythemia as one disease?

The similarities and the possible transitions between the two diseases have always been recognized.[4,5] Over the last few years, the interest in clarifying to what extent they share common pathogenetic mechanisms and clinical manifestations has been increased by the demonstration that a single somatic mutation of the Janus kinase 2 (*JAK2*) gene can be found in the large majority of polycythemia vera patients while the same mutation is present in only about half of those with essential thrombocythemia.[6,7] In particular, much effort has been devoted to investigating the possible role of *JAK2* mutational status in the heterogeneity of essential thrombocythemia subjects. This heterogeneity includes clonality of proliferation and type of clinical manifestations.[8,9] Recently, the results of a large prospective clinical study provided evidence that *JAK2*-positive essential thrombocythemia patients have a clinical phenotype similar to that of polycythemia vera subjects while being different from that of *JAK2*-negative subjects also as regards their response to anagrelide and hydroxyurea treatment.[10] Based on these results, the authors defined *JAK2*-positive essential thrombocythemia and polycythemia vera as two expressions of the same disease in which the degree of erythrocytosis may depend on biological or genetic modifiers. Grouping polycythemia vera subjects and *JAK2*-positive essential thrombocythemia patients into a single cohort may help in the organization of clinical studies which, in these relatively rare diseases, have the problem of limited numbers of recruitable patients. Certainly, an analysis based also on *JAK2* status would have added further interest to the data provided by De Stefano *et al*. Nevertheless, in this study, the combination of the two subgroups of essential thrombocythemia and polycythemia vera subjects with a past history of thrombosis seems justified by the fact that, notwithstanding the likely heterogeneity of the *JAK2* status and burden, the two populations showed remarkable similarities.

How to estimate the vascular risk and choose the best antithrombotic strategy

Polycythemia vera and essential thrombocythemia subjects are usually identified as having a low, intermediate or high vascular risk mostly on the basis of age and past thrombotic history.[11,12] This stratification does not, however, seem adequate to guide treatment decisions, which are better oriented by the four risk categories reported in Table 1. This latter risk stratification has the advantage of more clearly identifying two subgroups of patients, i.e. those at low risk and very high risk, for whom the current treatment options are uncertain and unsatisfactory, respectively. The assignment of a patient to a certain risk level is based tentatively on a simple scoring system (Table 2). This has the advantage of considering the impact of age in a more plausible progressive manner than that based on a single threshold level. Other risk factors are a past history of thrombosis, smoking and high leukocyte count, whose role has been shown by large clinical studies.[13-15] In addition, other classical risk factors are tentatively considered although these have a less clearly established role in this specific setting, likely due their limited prevalence in this population and/or to the relatively small size of many studies.[13-16] The scoring system includes a platelet count

Table 1. Risk stratification and treatment options in polycythemia vera and essential thrombocythemia.

Score	*Risk level*	*Suggested treatment*		*AR*
		Polycythemia vera	*Essential thrombocythemia*	
<1	Low	Phlebotomy Consider aspirin	Consider aspirin	<1.5
1-3	Moderate	Phlebotomy Aspirin	Aspirin Consider cytoreduction using interferon or hydroxyurea	1.5-3
3.1-5.5	High	Aspirin Hydroxyurea	Aspirin Hydroxyurea	3.1-6
> 5.5	Very high	Aspirin Hydroxyurea Consider more aggressive treatment	Aspirin Hydroxyurea Consider more aggressive treatment	>6

AR: approximate absolute risk (%patients/years).

above 10^{12}/L as a risk factor only because there is wide consensus on considering marked thrombocytosis an indication for cytoreduction. Finally, the table reports the approximate risk levels which, in these patients, may range from less than 1.5% to more than 6% (up to approximately 10%) *per annum*, as well as the main treatment recommendations.

These recommendations do not include interventions on life style and all modifiable factors because these apply uniformly to all patients. The role of these factors is frequently neglected, as happens in other thrombophilic states, because of the tendency to consider thrombosis as *caused* by the single specific condition rather than by an interplay of multiple factors. The presence of a myeloproliferative disorder should, however, increase efforts to identify and treat any additional risk factors and encourage the patient to adopt a healthy life-style. Particular attention should be given to smoking, which has an important effect on vascular risk and was found to be surprisingly common among polycythemia vera patients recruited in the ECLAP observational study.[15] Successful changes in modifiable risk factors require full co-operation from the patient and this underlines the importance of sharing treatment decisions and goals with the patient.

Treatment of blood hyperviscosity remains a primary objective in polycythemia vera subjects although recent findings indicated that the target values for this treatment might safely be higher than those generally accepted.[17] While waiting for confirmation of this it seems prudent to recommend, as rational targets, hematocrit values of 0.42 and 0.45 for female and male subjects, respectively.

As reported in Table 1, in low risk subjects the risks and benefits of low-dose aspirin should be carefully balanced in the individual patient. In fact, since the benefits of chronic aspirin administration are proportional to the vascular risk while the harm is independent of the risk level in a population in which the vascular risk is below a certain value bleeding events caused by aspirin may well exceed the vascular events prevented by this drug.[18]

Table 2. Scoring system.

Risk factor	*Score*
Age <40	0
40-55	1
56-65	2.5
>65	3.5
Hypertension	0.5
Dyslipidemia	0.5
Platelet count (>1000x10^9/L)	1
Leukocyte count (>12x10^9//L)	1
Smoking	1.5
Diabetes	1.5
Past history of thrombosis	3.5

This reasoning particularly applies to low risk essential thrombocythemia patients, in whom, in addition, low-dose aspirin has never been tested. The antithrombotic efficacy of aspirin, demonstrated in polycythemia vera subjects, can likely be extended to *JAK2*-positive essential thrombocythemia subjects; in addition, we do not have evidence that *JAK2*-negative essential thrombocythemia patients may be less sensitive to this agent. The small bleeding risk associated with the use of aspirin shown in the ECLAP study might underestimate the risk in the whole polycythemia vera population due to the fact that a significant percentage (24%) of polycythemia vera subjects evaluated by the ECLAP centers were excluded from the trial as they were judged to have a contraindication to aspirin, mostly because of gastrointestinal symptoms.[1] Such symptoms are known to be associated with an increased risk of upper gastrointestinal complications from aspirin use.[18] Thus, the risks of aspirin may be moderately higher than those found in the ECLAP study and this needs to be taken into consideration when choosing treatment for a low

risk population which, as defined in Table 1, can be estimated to have a vascular risk below the threshold level recommended for aspirin use in the general population.[18] In these low-risk patients, the decision on whether to prescribe aspirin must be taken after considering the patient's history of bleeding, gastrointestinal symptoms and other factors that may influence the thrombotic and/or hemorrhagic risk. These factors, in the particular setting of essential thrombocythemia subjects, include the *JAK2* status, the platelet count and the presence of microcirculatory symptoms, which are generally sensitive to aspirin. Aspirin is indicated for patients at moderate risk and is strongly recommended for subjects at higher risk levels. The so-called contraindications to aspirin should be carefully weighed in patients at high or very high risk because the absolute benefits of aspirin use in these patients are also expected to be high. In this view, among the patients with a past history of thrombosis, aspirin users should constitute a much higher percentage than that recorded in the retrospective analysis by Stefano *et al.* In fact, even when the patient has a history of a complicated ulcer, co-administration of a proton pump inhibitor can allow relatively safe use of aspirin[19,20] if this treatment is strongly required.

While phlebotomy is the treatment of choice in moderate risk polycythemia vera subjects, essential thrombocythemia subjects at the same risk level can be considered for pharmacological cytoreduction with agents other than hydroxyurea, such as interferon. Hydroxyurea is indicated in high risk subjects and absolutely recommended in very high risk subjects of any age. However, available data, including those from De Stefano *et al.*, suggest that while hydroxyurea is quite commonly used in relatively low risk subjects[1,15] it is not as widely used as expected in patients at very high risk. The latter finding also suggests that in many high risk patients cytoreductive therapy is not adequately aggressive, as demonstrated by the high levels of various hematologic parameters in patients receiving chemotherapy. Altogether the above findings indicate that current practice results in quite uniform pharmacological interventions across very different risk levels with the tendency to use treatments that are too aggressive in patients at low risk and too mild in those at very high risk.

Secondary prevention: does the type of first thrombotic event matter?

A past history of thrombosis has an important predictive role in patients with polycythemia vera and essential thrombocythemia. Furthermore, recurrences generally occur in the same district as that of the first vascular event, as shown by both the data from De Stefano *et al.* and by the ECLAP observational cohort study[15] .This raises the issue of whether secondary prevention strategies should be differentiated according to the type of the first event. In the general population secondary prevention of venous thrombosis relies on short or long term anticoagulation while secondary prevention of arterial events is largely based on aspirin. The latter may be associated with clopidogrel in acute coronary syndrome[21,22] or with dipyridamole after an ischemic stroke or transient ischemic attacks.[23,24] Whether these recommendations also apply to polycythemia vera and essential thrombocythemia patients is unclear. Certainly

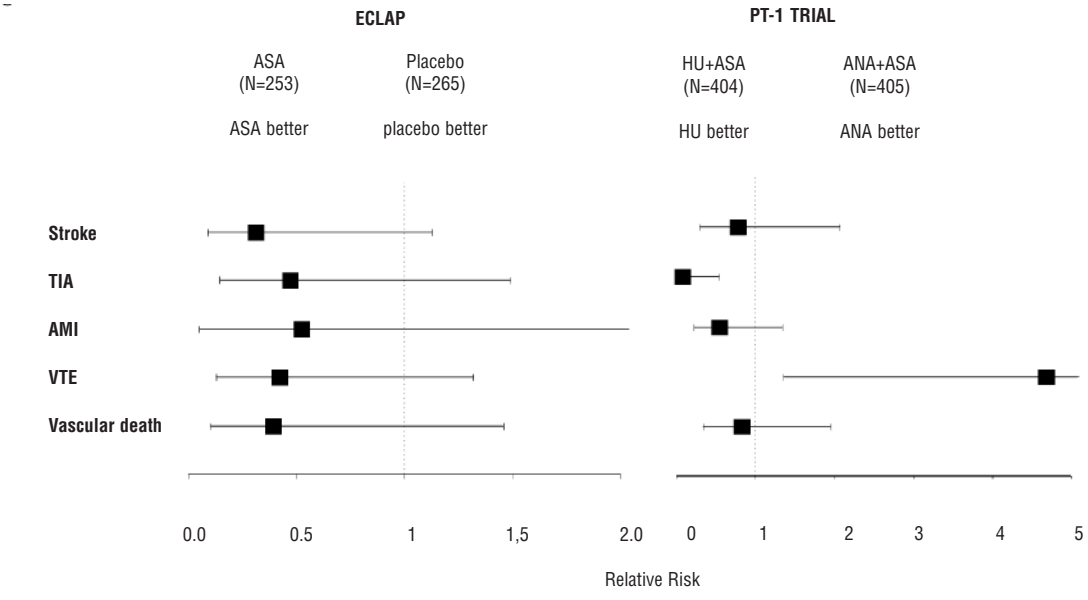

Figure 1. Point estimates and confidence intervals of relative risks for different vascular events in patients randomized in the ECLAP[1] and PT-1 trial.[27] N: number of patients; ASA: aspirin; HU: hydroxyurea; ANA: anagrelide; TIA: transient ischemic attack; AMI: acute myocardial infarction; VTE: venous thromboembolism.

many of these patients are being given clopidogrel after an acute coronary syndrome or a percutaneous revascularization procedure but no data are available as to a differential efficacy or safety of clopidogrel in this specific setting. This is an important issue since several findings indicate that the thrombotic diathesis of polycythemia vera and essential thrombocythemia patients may have, in comparison to that of the general population, peculiar features which include increased sensitivity to aspirin. In fact, in this specific setting, aspirin has an efficacy on venous and cerebrovascular events not found in other clinical conditions, which may be related to the suggested role of thromboxane hyperproduction in the thrombophilic state of these patients.[25,26] The efficacy of aspirin in preventing venous thromboembolism is suggested both by data from the ECLAP study (Figure 1) and by the retrospective analysis by De Stefano *et al.* The retrospective nature of the latter study and the limited number of events recorded in the ECLAP study are important limitations but undoubtedly the two findings point in the same direction. Future studies will have to explore this issue as well as that of the apparent limited efficacy of hydroxyurea in preventing venous thromboembolism reported in the PT1 trial[27] (Figure 1). The hypothesis raised by De Stefano's data concerning a limited efficacy of chemotherapy in patients with previous cerebrovascular event does not seem confirmed by the findings of the PT1 trial (Figure 1) which indicated that, in aspirin-treated patients, hydroxyurea provides greater protection than anagrelide against cerebrovascular events. We should be aware of the limitations of these comparisons which include limited numbers of events and differences in both study design and outcome measures. However, since there is no convincing evidence of a differential efficacy of aspirin and hydroxyurea in the various arterial districts, both patients with previous stroke or transient ischemic attacks and those with previous myocardial infarction should be treated with these two agents with a possible indication for more aggressive use of hydroxyurea in subjects with previous myocardial infarction and persistent leukocytosis. Patients with venous thrombosis are best treated with short-term anticoagulation, which may be more prolonged when thrombosis manifests at unusual sites, followed by long-term use of hydroxyurea and aspirin.

Conclusions and perspectives

The search for new strategies for high risk polycythemia vera and essential thrombocythemia subjects has undoubtedly become a priority for future research. Early recognition of the myeloproliferative disorder and wider use of aspirin and cytoreduction have likely contributed to lowering the incidence of thrombotic events. However, the rate of thrombotic recurrences in patients with a history of thrombosis remains unacceptably high. Physicians' awareness of such a high risk needs to be increased in order to avoid overestimating the neoplastic risk of hydroxyurea in relatively young subjects and/or of the bleeding risk in patients with gastrointestinal symptoms. In addition, in very high risk patients, the association of hydroxyurea and aspirin, which is currently viewed as an aggressive treatment, does not seem well suited to the patients' risk level, which calls for the adoption of more aggressive antithrombotic or cytoreductive strategies or for the search for novel treatment approaches. The retrospective analysis by De Stefano *et al.* suggests that the thrombotic risk is highest in the 2 years after the first thrombotic event and slowly declines thereafter. This finding is not unexpected since similar observations have been made in the general population following both arterial and venous thrombotic events. It likely reflects the decrease in hemostatic activation in the affected districts as well as the effect of treatment. In the particular setting of chronic myeloproliferative disorders, one has also to consider that the event generally leads to therapeutic interventions which gradually modify the disease-related parameters. On this basis, more aggressive antithrombotic therapy, based on the combination of aspirin with clopidogrel in patients with previous myocardial infarction, or with dypyridamole in patients with previous transient ischemic attacks or stroke, might be most beneficial in the 3 to 4 years following the thrombotic event.

Certainly, testing different treatment approaches in various subgroups of patients would be extremely difficult and thus clear priorities must be established, possibly based on pilot studies with biological end-points. Interestingly clopidogrel has been reported to reduce parameters of leukocyte activation[28] and thus its use may be more appropriate in patients with myeloproliferative disorders in whom the thrombophilic state is increasingly attributed to platelet and leukocyte activation and to platelet-leukocyte interactions (Figure 2).[29,30]

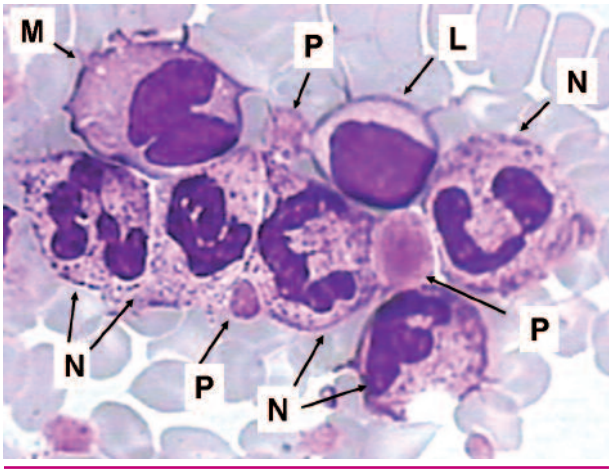

Figure 2. Platelet-leukocyte aggregates in a peripheral blood smear (May-Grünwald Giemsa, x100) of a patient with polycythemia vera (*courtesy of G. Zini*). P: platelet; N: neutrophil; M: monocyte; L: lymphocyte.

Further studies must clarify mechanisms underlying these phenomena and find novel strategies for monitoring and modulating these events.

Finally, most investigators are placing much expectation on *JAK2* inhibition as a rational approach for targeting an important mechanism leading to uncontrolled cell growth and possibly involved in the pathogenesis of the hemostatic imbalance. Several pharmaceutical companies have developed small molecule inhibitors which will soon enter phase 2 studies. Whether these agents can effectively control cell proliferation might soon be established. However, the safety of these inhibitors and their capacity to reduce disease progression and thrombotic complications will require long-term studies. While waiting for the development of such promising new therapies, every effort must be made to optimize the use of available drugs.

References

1. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 2004;350:114-24.
2. Streiff MB, Smith B, Spivak JL. The diagnosis and management of polycythemia vera in the era since the Polycythemia Vera Study Group: a survey of American Society of Hematology members' practice patterns. Blood 2002;99:1144-9.
3. De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, et al. for the GIMEMA CMD-Working Party. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Haematologica 2008; 93:372-80.
4. Spivak JL, Barosi G, Tognoni G, Barbui T, Finazzi G, Marchioli R, et al. Chronic myeloproliferative disorders. Hematology Am Soc Hematol Educ Program 2003;200-24.
5. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol 2005;128:275-90.
6. Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell 2005;7:387-97.
7. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 2005;352: 1779-90.
8. Wolanskyj AP, Lasho TL, Schwager SM, McClure RF, Wadleigh M, Lee SJ, et al. JAK2 mutation in essential thrombocythaemia: clinical associations and long-term prognostic relevance. Br J Haematol 2005;131:208-13
9. Kittur J, Knudson RA, Lasho TL, Finke CM, Gangat N, Wolanskyj AP, et al. Clinical correlates of JAK2V617F allele burden in essential thrombocythemia. Cancer 2007;109: 2279-84.
10. Campbell PJ, Scott LM, Buck G, Wheatley K, East CL, Marsden JT, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet 2005;366:1945-53.
11. Finazzi G, Barbui T. How I treat patients with polycythemia vera. Blood 2007;109:5104-11.
12. Gangat N, Wolanskyj AP, McClure RF, Li CY, Schwager S, Wu W, et al. Risk stratification for survival and leukemic transformation in essential thrombocythemia: a single institutional study of 605 patients. Leukemia 2007;21:270-6.
13. Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol 2005;23:2224-32.
14. Carobbio A, Finazzi G, Guerini V, Spinelli O, Delaini F, Marchioli R, et al. Leukocytosis is a risk factor for thrombosis in essential thrombocythemia: interaction with treatment, standard risk factors and Jak2 mutation status. Blood 2007;109:2310-3.
15. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood 2007; 109:2446-52.
16. Watson KV, Key N. Vascular complications of essential thrombocythaemia: a link to cardiovascular risk factors. Br J Haematol 1993;83:198-203.
17. Di Nisio M, Barbui T, Di Gennaro L, Borrelli G, Finazzi G, Landolfi R, et al. The haematocrit and platelet target in polycythemia vera. Br J Haematol 2007;136:249-59.
18. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353:2373-83.
19. Chan FKL, Ching JYL, Hung LCT, Wong VWS, Leung VKS, Kung NNS, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005;352:238-44.
20. Liberopoulos EN, Elisaf MS, Tselepis AD, Archimandritis A, Kiskinis D, Cokkinos D, et al. Upper gastrointestinal haemorrhage complicating antiplatelet treatment with aspirin and/or clopidogrel: where we are now? Platelets 2006;17:1-6.
21. Ramanath VS, Eagle KA. Evidence-based medical therapy of patients with acute coronary syndromes. Am J Cardiovasc Drugs 2007;7:95-116.
22. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. Circulation 2004;110:1202-8.
23. ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomized controlled trial. Lancet 2006 20;367: 1665-73.
24. Ariesen MJ, Algra A, Kappelle LJ. Antiplatelet drugs in the secondary prevention after stroke: differential efficacy in large versus small vessel disease? A subgroup analysis from ESPS-2. Stroke 2006;37:134-8.
25. Landolfi R, Ciabattoni G, Patrignani P, Castellana MA, Pogliani E, Bizzi B, Patrono C. Increased thromboxane biosynthesis in patients with polycythemia vera: evidence for aspirin-suppressible platelet activation in vivo. Blood 1992;80:1965-7.
26. Rocca B, Ciabattoni G, Tartaglione R, Cortelazzo S, Barbui T, Patrono C, Landolfi R. Increased thromboxane biosynthesis in essential thrombocythemia. Thromb Haemost 1995;74:1225-30.
27. Harrison CN, Campbell PJ, Buck G, Wheatley K, East CL, Bareford D, et al. United Kingdom Medical Research Council Primary Thrombocythemia 1 Study. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 2005;353:33-45.
28. Evangelista V, Manarini S, Dell'Elba G, Martelli N, Napoleone E, Di Santo A, et al. Clopidogrel inhibits platelet-leukocyte adhesion and platelet-dependent leukocyte activation. Thromb Haemost 2005;94:568.
29. Falanga A, Marchetti M, Vignoli A, Balducci D, Barbui T. Leukocyte-platelet interaction in patients with essential thrombocythemia and polycythemia vera. Exp Hematol 2005;33:523-30.
30. Falanga A, Marchetti M, Evangelista V, Vignoli A, Licini M, Balicco M, et al. Polymorphonuclear leukocyte activation and hemostasis in patients with essential thrombocythemia and polycythemia vera. Blood 2000;96:4261-6.