Polycythemia Vera and Acute Coronary Syndromes: Pathogenesis, Risk Factors and Treatment

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Abstract

Polycythemia vera is a chronic myeloproliferative disorder marked by significant thrombotic complications. Myocardial infarction and heart failure is the most common cause of death. Mechanisms involved in the pathogenesis of these complications are not yet well elucidate; erythrocytosis and quantitative platelet abnormalities may play a major role in the development of thrombosis and ischemia. Age older than 60 years and prior history of thrombosis are the two main risk factors. Evidence for the prevention and treatment of specific cardiovascular complications in PV is too scarce. However, current evidence supports the use of hydroxyurea as the initial choice of cytotherapeutic agent in PV patients with acute coronary syndrome.

Keywords: Myocardial infarction; Polycythemia vera; Pathogenesis; Risk factors; Prevention; Treatment

Introduction

Polycythemia Vera (PV) is a chronic myeloproliferative disorder, involving a multipotent hematopoietic progenitor cell, which causes in general an increased production of red cells, granulocytes and platelets, but most significantly in erythrocytes, which leads to hyperviscosity and an increased risk of thrombosis.

Bleeding, thrombotic, and vascular complications are the major causes of morbidity and mortality in PV, occurring in 40 to 60% of the patients [1,2]. Myocardial infarction (MI) and heart failure is the most common cause of death [3].

The pathophysiology of thromboembolic events in polycythemia Vera has not been elucidated, but many factors are involved: increases in hematocrit and blood hyperviscosity, stimulation of platelet aggregation and thrombogenesis, the presence of leukocytosis, rigidity of the membrane and intimal proliferation [4-6].

Advanced age and a prior history of thrombosis are the two most important risk factors for vascular complications; hypercholesterolemia, hypertension, smoking, and diabetes have been recognized as predictors of thrombosis [7-10]. Furthermore, thrombosis often complicates treatment in patients with PV and modest hematocrit elevations (50-60%) [11].

Myocardial infarction and sudden death are complications of newly diagnosed or untreated PV; they occur most often in elderly people (≥ 65 years) with underlying coronary artery disease [12,13]. However, younger patients with PV who are free from coronary artery disease can also be affected, and sometimes the outcome is death [12,13].

Cytoreductive treatment of blood hyperviscosity by phlebotomy or chemotherapy and antiplatelet therapy with low-dose aspirin have dramatically reduced the number of thrombotic complications and substantially improved survival [14].

This review highlights recent breakthroughs in the pathogenesis, risk factors, prevention, and treatment of myocardial infarction in PV.

Pathogenesis

Thrombotic occlusion of large arterial vessels is also a frequent finding in PV and generally involves cerebral and coronary vessels. Acute coronary syndromes have been often reported to occur in patients without risk factors and with normal coronary arteries [13,15-17].

Several mechanisms are implicated:

Erythrocytosis

The hematocrit is the major determinant of whole blood viscosity, increased hematocrit level is associated with decreased cerebral blood flow rate and contribute to the thrombotic tendency in PV. In addition to increased blood viscosity, the axial migration of red cells occurs with displacement of platelets to the mural plasmatic zone, exposing them to maximal vessel wall shearing forces; erythrocytosis enhances platelet-vascular interactions, especially at the high shear rates found in arterioles and capillaries [18]. The increased mass of red cells in PV may also contribute to heightened platelet activation [19].

Nevertheless, the hemorrhheologic effects of erythrocytosis cannot be the only explanation for the thrombotic tendency in PV; comparable or even greater degrees of secondary erythrocytosis are not associated with thrombosis, and even normalization of the hematocrit in PV does not fully protect against the risk of thrombosis [4].

Quantitative platelet abnormalities

Thrombocytosis may contribute to the pathogenesis of myocardial infarction in PV, particularly because platelet cytotherapeutic reduces the risk of recurrent thrombosis in high-risk patients. However, the degree of platelet count has not been significantly correlated with thrombosis risk in PV [20,21].

Qualitative platelet abnormalities

A variety of structural and functional abnormalities of platelets have

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been reported in patients with myeloproliferative diseases, including abnormal expression of platelet membrane glycoproteins, spontaneous platelet aggregation and circulating platelet aggregates; increased platelet microparticles; acquired storage pool disease and other structural and biochemical abnormalities [1,5]. Unfortunately, none of these qualitative platelet defects has been convincingly demonstrated to be causally associated with either thrombotic or bleeding complications in PV.

**Leucocytes**

The role of leucocytes in the pathogenesis of vascular events is increasingly recognized.

In addition, in patients with atherosclerotic vascular disease, leucocytosis has been associated with an increased thrombotic risk. Because leucocytosis characterizes many PV subjects, it has been hypothesized to be a potential determinant of their thrombotic risk [1,5].

In PV these cells have an increased tendency to activate and to form platelet-leucocyte aggregates, particularly in subjects with a thrombotic history thus suggesting that leucocytes and platelets, which share the same clonal origin, might have similar functional abnormalities that might also give rise to a complex interplay [22,23].

However, further research is needed to explore the possible role of qualitative leucocyte defects in the vascular ischemic complications of this disorder.

**Other possible mechanisms**

Recently, it has been reported that bone marrow hematopoietic stem cell–derived endothelial progenitors can migrate to areas of vascular injury or ischemia and repopulate the initial surfaces of the vessel wall as differentiated endothelial cells [24,25].

It is possible, that hemostatically defective endothelial cells, derived from abnormal hematopoietic stem cell clones in PV might also play a role in the clinical bleeding and thrombotic complications.

Erythropoietine (Epo) levels are persistently decreased in PV, and this hormone is now recognized to have non-erythroid functions that are mediated by expression of Epo and its receptor in many other tissues, including the cardiovascular system [26,27]. Therefore, Chronic “Epo deficiency” that occurs in PV patients might enhance cerebral and cardiac infarction.

Recently, the influence of the JAK2 V617F mutational load on the thrombotic risk has been evaluated in patients with PV. This analysis indicated that the JAK2 V617F/JAK2 wild-type ratio behaved as an independent risk factor for major vascular events (p=0.027) [28].

**Risk Factors**

The evaluation of the vascular ischemic risk in PV subjects is based on a combination of established criteria, widely used in these patients [5,7]. Tentative stratifications of thrombotic risks of PV are reported in table 1.

| Risk level | Factors                                      |
|------------|----------------------------------------------|
| High       | Age ≥ 60 years or previous thrombosis or diabetes |
| Intermediate | Age > 40 to <60 years plus one risk factor* or age < 40 years plus two risk factors* |
| Low        | None of the above                            |

* Risk factors: smoking, hypertension, hypercholesterolemia. Diabetes is considered a major risk factor, equivalent to a previous thrombosis or to advanced age.

**Table 1: Thrombotic risk level in PV patients.**

**Age**

Age is a general risk factor for thrombosis under any circumstance [29]. Barbui et al. have reported in a large PV epidemiologic study (n=1638), a hazard ratio of vascular complications of 8.6 for patients older than 60 years than in younger patients (p=0.0001) [30]. More recent, In the ECLAP (European Collaboration on Low dose Aspirin in Polycythemia) study, the incidence of cardiovascular complications was higher in patients aged more than 65 years (5.0% per patient-year, hazard ratio 2.0, 95% confidence interval [CI] 1.22–3.29, p<0.006) [9].

**History of thrombosis**

A prior history of thrombosis has been indicated as a factor significantly contributing to the overall risk of thrombosis in PV. In the ECLAP study, the incidence of cardiovascular complications was higher in patients with a history of thrombosis (4.93% per patient-year, hazard ratio 1.96, 95% CI 1.29–2.97, p<0.0017) than in younger subjects with no history of thrombosis (2.5% per patient-year, reference category). Patients with a history of thrombosis and who were aged over 60 years had the highest risk of cardiovascular events during follow-up (10.9% per patient-year, hazard ratio 4.35, 95% CI 2.95–6.41, p<0.0001) [9].

These data confirm previous findings that increasing age and a history of thrombosis are the two most important prognostic factors for the development of vascular complications [8,31].

**Cardiovascular risk factors**

Smoking, hypertension, congestive heart failure, hypercholesterolaemia, diabetes mellitus were other significant risk factors for thrombosis that have been assessed in multiple studies. The role of these minor factors is partially derived from the ECLAP observational study.

This analysis indicates that hypertension and smoke play an important role as risk factors for myocardial infarction and stroke; the role of other risk factors could not be determined because of the very large number of patients and events required for these analyses [30-32]. When present in a young patient without prior thrombosis (‘low-risk’ patient), these factors define an ‘intermediate risk’ category. This classification forms the rationale for the indication of therapy [9].

**Prevention and Treatment**

Evidence for the prevention and treatment of specific cardiovascular complications in PV is too scarce. In general, the treatment of acute coronary syndromes secondary to chronic myeloproliferative disorders require special attention in maintaining the delicate balance between the risk of bleeding and clotting tendency.

**Correction of cardiovascular risk factors**

The identification and appropriate management of cardiovascular risk factors and the promotion of a healthy lifestyle in PV, as in the general population, should be considered a cornerstone of vascular prevention. However, a definitive causative/contributory role for CV risk factors on the incidence of vascular events in PV is not yet defined, except for smoking [5]. Therefore, particular attention has to be given to smoking habit which has an important effect on vascular risk and
which was found to be surprisingly common among PV patients recruited in the ECLAP observational study [30].

**Antiplatelet therapy**

The prevention of vascular risk is the foremost objective thrombotic treatment of PV. In the ECLAP study, the efficacy and safety of low-dose aspirin to prevent thrombotic complications in patients with PV was assessed, data analysis showed a significant reduction of a primary combined end-point including cardiovascular death, non-fatal myocardial infarction, non fatal stroke and major venous thromboembolism (relative risk: 0.4; [95% CI: 0.18–0.91], p=0.0277) [33]. However, it is important to underline that the ECLAP trial was conducted in a relatively low risk population.

In a review from 86 studies, Willoughby et al. found that prophylactic aspirin use in patients with polycythemia vera reduced the occurrence of major vascular events by 22% and nonfatal myocardial infarction by 30% [34].

Based on these data, it can be inferred that initiating therapy with aspirin up to a maximum dose of 300 mg in PV patients who present with an acute coronary syndrome and then quickly reducing the dose to 100 mg by discharge for long-term prophylactic use would provide the greatest benefit in mortality reduction with a minimal risk for bleeding.

**Cytoreductive therapy**

The purpose of prophylactic cytoreduction in managing patients with PV is to reduce the risk of thrombosis, which accounts for the morbidity and mortality associated with the disease. Phlebotomy and myelosuppression are the treatment options most often utilized, either alone or in combination. Phlebotomy to maintain hematocrit at &lt;45% in males and &lt;42% females remains the cornerstone of therapy for all patients with PV. In addition to treatment with phlebotomy in PV, myelosuppressive agents such as hydroxyurea should be considered in patients who are considered at high risk for thrombosis [30].

Recently, Marchioli et al. showed that maintaining a hematocrit target of 45 to 50% in patients receiving conventional treatment (including phlebotomy, hydroxyurea, or both) was associated with four times the rate of death from cardiovascular causes or major thrombosis, as was maintaining a hematocrit target of less than 45%. The incidence of the primary end point was 1.1 events per 100 patient-years in the low-hematocrit group, as compared with 4.4 events per 100 patient-years in the high hematocrit group [35].

Appropriate cytoreduction with the goal to optimize the control of the blood cell counts is recommended in all patients with acute vascular events [36,37].

**Anticoagulation**

Treatment with Oral Anticoagulants (OA) may be promising as an antithrombotic strategy in patients with PV. However, no clinical studies have been carried out to evaluate the efficacy of OA in prevention and treatment of vascular complications of patients with PV.

Anti-vitamin K agents was found to be independently effective in preventing recurrent thrombosis in PV. De Stefano et al. have reported that long-term treatments with antiplatelet or anti-vitamin K agents prevent independently recurrence, with reductions of re-thrombosis of 58% and 68%, respectively. In contrast, the association of antiplatelet agents plus vitamin K antagonists resulted in a higher incidence of major bleeding (2.8% patient-years) [38]. Recent guidelines therefore recommend oral anticoagulation in venous thrombosis for 3–6 months in PV and essential thrombocythemia (ET) patients [39].

**New oral anticoagulants**

New oral anticoagulants may replace warfarin (anti-vitamin K) in prophylaxis of thrombosis in PV. Apixaban and rivaroxaban are selective factor Xa inhibitors while dabigatran is a direct thrombin inhibitor. Compared to warfarin, the newer oral anticoagulants are associated with several advantages. These new agents do not require anticoagulation monitoring and they have limited food- and drug-drug interactions due to their minimal metabolism through the CYP450 system. Of special interest in the setting of PV is the fact that the bleeding complications seem to be lower compared with vitamin-K antagonist [39].

**Anagrelide**

It is a nonleukemogenic drug that relatively selectively inhibits megakaryocyte proliferation and differentiation. However, in a head-to-head study between HU and anagrelide plus low-dose aspirin in both arms, anagrelide was inferior to HU in terms of response and safety.

Patients in the anagrelide arm showed an increased rate of arterial thrombosis, major bleeding and myelofibrotic transformation but a decreased incidence of venous thrombosis compared to HU. In addition, anagrelide was more poorly tolerated than HU and presented significantly greater rates of cardiovascular, gastrointestinal, neurological and constitutional complications [30].

**Pipobroman**

Patients with PV may also be treated with pipobroman, a bromide derivative of piperazine. Recent reports demonstrates, in a large series of patients homogeneously treated and observed for a long period, that pipobroman is an effective and well tolerated agent for the control of PV, with a relatively low risk of early thrombotic complications (6% at 3 years) [40]. Hematologic evolution to myelofibrosis was found to be higher in patients treated predominantly with HU (32% at 20 years) compared with those treated with pipobroman. (32% at 20 years) [41].

**Interferon alpha (IFN-αlpha)**

IFN-αlpha was considered for the treatment of patients with myeloproliferative disorders since this agent suppresses the proliferation of hematopoietic progenitors. It is now well established that IFN-α can control erythrocytosis or thrombocytosis in the majority patients with PV or ET. Its widespread use was offset by its parenteral administration, cost, and toxicity although, and the largest study of IFN- with long-term follow-up reported to date [42] the frequency of treatment discontinuation resulting from toxicity was only 15% when low doses were used. Furthermore, no vascular event was recorded with the use of IFN.

**Tyrosine Kinase Inhibitors (TKIs)**

Many recent reports have showed that therapy with TKIS (Imatinib, dasatinib, nilotinib) was generally well tolerated in PV patients. Nevertheless, Ribero et al. have found that even if Imatinib was not related to systematic deterioration of cardiac function, there is still a possibility of isolated cases of cardiotoxicity [43]. There is scarce information about cardiotoxicity of dasatinib and nilotinib. Being aware of the risk of using these drugs and a close relationship between haematologists/oncologists and cardiologists is particularly important to early detect and institute the appropriate treatment to prevent irreversible myocardial injury [44].

**New drugs**

The JAK2V617F mutation, a point mutation in the tyrosine kinase
gene JAK2 (Janus Kinase 2), has emerged as a central feature in the pathogenesis of PV. The diagnostic criteria of PV have been revised in 2008 and include the JAK2V617F mutation as one of the two major criteria of the disease. Thus, a significant number of new drugs with JAK 2 target are currently at varying stages of clinical evaluation, especially in patients with PV/ET refractory or intolerant to conventional therapy. Recently Ruxolitinib (a JAK1 and JAK2 inhibitor) became the first-in-class JAK inhibitor to receive approval by the Food and Drug Administration for use in intermediate-2 and high-risk myelofibrosis [30].

Coronary reperfusion

The safety and efficacy of fibrinolytic therapy as the exclusive treatment of an acute coronary syndrome in patients with polycythemia vera is unknown. Furthermore, effective fibrinolytic therapy may be undermined by residual coronary thrombus, which potentially may be seen in polycythemia vera patients who have high platelet counts [45].

However, Ruggeri et al. demonstrated that controlling blood counts in PV patients undergoing coronary artery bypass grafting reduced but did not eliminate the risk for postoperative thrombosis and hemorrhage [46].

Treatment Strategy

In a patient with myeloproliferative disease, an acute venous thrombosis is managed in the standard fashion (heparin followed by oral anticoagulant therapy). However, systemic anticoagulation alone in PV may not be sufficient and concomitant myelosuppressive therapy with hydroxyurea is highly recommended [3,30]. Moreover, one of the principal factors to consider in choosing a therapy for myocardial infarction in patients with PV is the increased risk of bleeding associated with the use of thrombolytic therapy. Although, there are no current guidelines that address stent restenosis risk reduction or treatment of acute MI in PV patients, current evidence supports, in addition to the standard antiplatelet therapy, the use of hydroxyurea as the initial choice of cytoprotective agent in PV patients with acute coronary syndrome [47-54].

Conclusion

PV is a chronic myeloproliferative disorder characterized by a high risk of developing arterial and venous thromboembolic complications. In recent years, great insight has been gained into the understanding of the pathogenesis of thrombosis in PV. Nevertheless, the search for new strategies for management the cardiovascular events in PV patients has undoubtedly become a priority for future research.

References

1. Schäfer AI (1984) Bleeding and thrombosis in the myeloproliferative disorders. Blood 64: 1-12.
2. Murphy S, Iland H, Rosenthal D, Laszlo J (1986) Essential thrombocythemia: an interim report from the Polycythemia Vera Study Group. Semin Hematol 23: 177-182.
3. Venegoni P, Schroth G (1994) Myocardial infarction and polycythemia vera: how should we treat it? Cathech Cardiovasc Diagn 32: 259-261.
4. Schäfer AI (2006) Molecular basis of the diagnosis and treatment of polycythemia and essential thrombocythysis, Blood 107: 4214-4222.
5. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, et al. (2007) Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood 109: 2446-2452.
6. Hermans B, Handt S, Kindler J, Füzesi L (1998) Coronary vasculopathy in polycythemia vera. Pathol Oncol Res 4: 37-39.
7. Elliott MA, Tefferi A (2005) Thrombosis and haemorrhage in polycythemia vera and essential thrombocythemia. Br J Haematol 128: 275-290.
8. (1995) Polycythemia vera: the natural history of 1213 patients followed for 20 years. Gruppo Italiano Studio Policitemia. Ann Intern Med 123: 656-664.
9. Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, et al., et al. (2005) Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol 23: 2224-2232.
10. Passamonti F, Rumi E, Pugnolino E, Malabarba L, Bertazzoni P, et al. (2004) Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. Am J Med 117: 755-761.
11. Pearson TC, Wetherley-Mein G (1978) Vascular occlusive episodes and venous haematoctit in primary proliferative polycythemia. Lancet 2: 1219-1222.
12. Benjamin D, Yeshurun D, Chamnillas J, Pinkhas J (1978) Hyperlipidemia and myocardial infarction among 118 patients with polycythemia vera. Am J Med Sci 276: 23-26.
13. Chelmin MD, McAllister HA, de Castro CM (1975) Myocardial infarction without atherosclerosis. JAMA 231: 951-959.
14. Barbui T, Finazzi G (2006) Evidence-based management of polycythemia vera. Best Pract Res Clin Haematol 19: 483-493.
15. Hart RG, Kanter MC (1990) Hematologic disorders and ischemic stroke. A selective review. Stroke 21: 1111-1121.
16. Schäfer AI, Kroll MH (1993) Nonatheromatous arterial thrombosis. Annu Rev Med 44: 155-170.
17. Chelmin MD, McAllister HA, de Castro CM (1975) Myocardial infarction without atherosclerosis. JAMA 231: 951-959.
18. Pearson TC (1997) Hemorheologic considerations in the pathogenesis of vascular occlusive events in polycythemia vera. Semin Thromb Hemost 23: 433-439.
19. Vellas J, Santos MT, Aznar J, Martinez M, Moscardó A, et al. (2002) Platelet-erythrocyte interactions enhance alpha(IIb)beta(3) integrin receptor activation and P-selectin expression during platelet recruitment: down-regulation by aspirin ex vivo. Blood 99: 3978-3984.
20. Buss DH, Stuart JJ, Lipscomb GE (1985) The incidence of thrombosis and hemorrhagic disorders in association with extreme thrombocytosis: an analysis of 129 cases. Am J Hematol 20: 365-372.
21. Wehmeier A, Tschöpe D, Esser J, Menzel C, Neuenhuis HK, et al. (1991) Circulating activated platelets in myeloproliferative disorders. Thromb Res 61: 271-278.
22. Falanga A, Marchetti M, Evangelista V, Vignoli A, Lisci M, et al. (2000) Polymorphonuclear leukocyte activation and hemostasis in patients with essential thrombocythemia and polycythemia vera. Blood 96: 4261-4266.
23. Jensen MK, de Nuly Brown P, Lund BV, Nielsen OJ, Hasselbalch HC (2001) Increased circulating platelet-leukocyte aggregates in myeloproliferative disorders is correlated to previous thrombosis, platelet activation and platelet count. Eur J Haematol 66: 143-151.
24. Schattenman GC (2004) Adult bone marrow-derived hemangioblasts, endothelial cell progenitors, and EPCs. Curr Top Dev Biol 64: 141-180.
25. Urbich C, Dimmeler S (2004) Endothelial progenitor cells: characterization and role in vascular biology. Circ Res 95: 343-353.
26. Gassmann M, Heinike K, Soliz J, Ogunshola OO (2003) Non-erythroid functions of erythropoietin. Adv Exp Med Biol 543: 323-330.
27. Smith KJ, Bleyer AJ, Little WC, Sane DC (2003) The cardiovascular effects of erythropoietin. Cardiovasc Res 59: 536-548.
28. Vannucchi AM, Antonioli E, Guglielmelli P (2006) Influence of the JAK2V617F mutation on diagnostic on major clinical aspects in patients with polycythemia vera. Blood 108: 6a.
29. Rosendaal FR (1997) Risk factors for venous thrombosis: prevalence, risk, and interaction. Semin Hematol 34: 171-187.
30. Barbui T, Finazzi MC, Finazzi G (2012) Front-line therapy in polycythemia vera and essential thrombocythemia. Blood Rev 26: 205-211.
31. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, et al. (1986) Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. Semin Hematol 23: 132-143.
32. Tefferi A (2003) Polycythemia vera: a comprehensive review and clinical recommendations. Mayo Clin Proc 78: 174-194.
33. Landolfi R, Marchioli R, Kuti J, Giisslinger H, Tognoni G, et al. (2004) Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 350: 114-124.

34. Willoughby S, Pearson TC (1998) The use of aspirin in polycythemia vera and primary thrombocythaemia. Blood Rev 12: 12-22.

35. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, et al. (2013) Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med 368: 22-33.

36. Venegoni P, Cyprus G (1994) Polycythemia and the heart. A review. Tex Heart Inst J 21: 198-201.

37. McMullin MF, Bareford D, Campbell P, Green AR, Harrison C, et al. (2005) Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol 130: 174-195.

38. De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, et al. (2008) Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Haematologica 93: 372-380.

39. Reikvam H, Tiu RV (2012) Venous thromboembolism in patients with essential thrombocythemia and polycythemia vera. Leukemia 26: 563-571.

40. Passamonti F, Brusamolino E, Lazzerino M, Baraté C, Klersy C, et al. (2000) Efficacy of pipobroman in the treatment of polycythemia vera: long-term results in 163 patients. Haematologica 85: 1011-1018.

41. Kladjan JJ, Chevre S, Dosquet C, Chomienne C, Rain JD (2011) Treatment of polycythemia vera with hydroxyurea and pipobroman: final results of a randomized trial initiated in 1980. J Clin Oncol 29: 3907-3913.

42. Kladjan JJ, Cassinat B, Chevre S, Turlure P, Cambier N, et al. (2008) Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood 112: 3065-3072.

43. Ribeiro AL, Marcelino MS, Bittencourt NH, Barbosa MM, Nunes Mdo C, et al. (2008) An evaluation of the cardiotoxicity of imatinib mesylate. Leuk Res 32: 1809-1814.

44. García-Alvarez A, García-Albeniz X, Esteve J, Rovira M, Bosch X (2010) Cardiotoxicity of tyrosine-kinase-targeting drugs. Cardiovasc Hematol Agents Med Chem 8: 11-21.

45. Turakhia MP, Murphy SA, Pinto TL, Antman EM, Giugliano RP, et al. (2004) Association of platelet count with residual thrombus in the myocardial infarction-related coronary artery among patients treated with fibrinolytic therapy for ST-segment elevation acute myocardial infarction. Am J Cardiol 94: 1406-1410.

46. Ruggeri M, Rodeghiero F, Tosetto A, Castaman G, Scognamiglio F, et al. (2008) Postsurgery outcomes in patients with polycythemia vera and essential thrombocythemia: a retrospective survey. Blood 111: 866-671.

47. Gouri A, Yakhlef A, Dekaken A, Bentorki AA (2012) Acute myocardial infarction revealing a polycythemia vera. Ann Biol Clin (Paris) 70: 489-491.

48. Cucuianu A, Stoia M, Farcas A, Dima D, Zdrenghea M, et al. (2006) Arterial stenosis and atherothrombotic events in polycythemia vera and essential thrombocythemia. Rom J Intern Med 44: 397-406.

49. Rossi C, Randi ML, Zerbinati P, Rinaldi V, Girolami A (1998) Acute coronary disease in essential thrombocythemia and polycythemia vera. J Intern Med 244: 49-53.

50. Passamonti F (2012) How I treat polycythemia vera. Blood 120: 275-284.

51. Finazzi G, Barbui T (2007) How I treat patients with polycythemia vera. Blood 109: 5104-5111.

52. Hermanns B, Handt S, Kindler J, Füzesi L (1998) Coronary vasculopathy in polycythemia vera. Pathol Oncol Res 4: 37-39.

53. Altanasio S, Dallow RA, Nathan S (2011) ST-segment Elevation Myocardial Infarction in a Patient with Polycythemia Vera Managed with High-dose Tiroliban Pre-treatment, Aspiration Thrombectomy, and Paclitaxel-eluting Stent Implantation. US Cardiology 8: 86-69.

54. Tekin M, Gokaslan S, Diker E, Aydoqdu S (2008) [Development of acute coronary syndrome in three patients with essential thrombocythemia or polycythemia vera]. Turk Kardiyol Dern Ars 36: 35-38.