REVIEW ARTICLE

Polycythemia vera: Essential management protocols

Farah Ashraf Khan*, Riaz Ahmed Khan**, Muhammad Iqbal***, Safdar Hussain***

** Trainee Medical Officer, **Associate Professor and HoD,*** Consultant Anesthesiologist*
Department of Anesthesiology, Rehman Medical Institute, Peshawar (Pakistan)

Correspondence: Dr Riaz Ahmed Khan., Consultant Anesthesiologist, Rehman Medical Institute, Peshawar (Pakistan); Email: riaz_kmc75@yahoo.com

SUMMARY

Primary polycythemia (polycythemia vera) is a hematopoeitic stem cell disorder giving rise to proliferation of a clone of hematopoietic precursors leading to an excess production of erythrocytes with thrombocytosis and leukocytosis. The optimum management of polycythemia vera remains elusive. Patients requiring surgery are at increased risk of both perioperative thrombosis and hemorrhage. On one hand, thrombosis can lead to multi organ ischemia and infarction while on the other, bleeding diathesis can lead to profuse perioperative hemorrhage; both posing considerable risk to the patient's health and stress to the anesthesiologist concerned directly with perioperative management of the patient. Hence, management guidelines for polycythemia vera needs to be clearly understood and tailored to each patient individually and appropriate management protocols need to be defined accordingly.

Key words: Polycythemia vera; Stem cells; Erythrocytes; Erythrocytosis

Citation: Khan FA, Khan RA, Iqbal M, Hussain S. Polycythemia vera: Essential management protocols. Anaesth Pain & Intensive Care 2012;16(1):92-98

INTRODUCTION

Primary polycythemia (polycythemia vera) is a hematopoeitic stem cell disorder giving rise to proliferation of a clone of hematopoietic precursors leading to an excess production of erythrocytes with thrombocytosis and leukocytosis in some patients. Although the incidence of complications associated with polycythemia vera (PV) is low, yet the risk of perioperative morbidity and mortality is substantial if complications do occur. Focus of attention has always been on other hematological disorders, particularly anemia, despite lack of serious complications associated with anemia in the perioperative period. A shift of attention to less frequently encountered bleeding anomalies like PV should draw the attention of not only the anesthesiologist but also the physicians and surgeons directly involved with the patient concerned. This article discusses the various presentations of PV in the operating room at our hospital; despite a worldwide incidence of just 1%, we had an alarming 3 cases presenting for surgery in a period of 3 weeks. Therefore, vigilance and a thorough understanding of the pathophysiology of disease and its complications that can occur perioperatively becomes a paramount responsibility of the anesthetist. This article reviews the incidence, pathophysiology and morbidity associated with complications therein and predisposing risk factors associated with such complications. For selected scenarios, the value of an anesthesiologist performing a more extensive preoperative evaluation is described. The importance of using a multidisciplinary approach for the purpose of reducing intraoperative and postoperative distress of all parties involved in the patients care is reviewed. Several recommendations for the prevention of perioperative morbidity and a plan for its management are presented. Exercising an effective reduction strategy for known complications associated with PV can minimize expenses in terms of patient cost and hospital resources while maximizing anesthetic outcome and patient survival.

CLASSIFICATION

Polycythemia is classified into two groups: PV (PV primary or true) which is a disorder of the blood-producing cells of the bone marrow that results in overproduction of red blood cells. In polycythemia vera, the excess of red blood cells increases the volume of blood and makes it thicker, so that it flows less easily through small blood vessels. The cause remains unknown. Non Vera types are further subclasssified into secondary & relative polycythemia. The secondary are usually caused by oxygen deprivation, such as living at high altitudes, smoking, chronic pulmonary and cyanotic heart disease. Relative polycythemia is mainly due to dehydration which is caused by use of diuretics, drinking too little fluids or excessive sweating. All the non vera types have underlying causes and are not true PV.

INCIDENCE AND MORBIDITY

Although the incidence of PV varies worldwide, approximately 1.9 in 100,000 (person/year) are diagnosed each year. PV occurs in all age groups, [1] although the incidence increases with age. One study found the median age at diagnosis to be 60 years, [2] while a Mayo Clinic study in Olmsted County, Minnesota found that the highest incidence was in people aged 70–79 years.[3] The overall incidence in this study population was 1.9 per 100,000 person-years, and the disease was more common in men than women.[3] The major causes of morbidity and mortality associated with PV are as follows:

- Thrombosis has been reported in 15-60% of patients, depending on the control of their disease. It is the major cause of death in 10-40% of patients. Venous thromboses have resulted in pulmonary emboli, renal failure from renal vein or artery thrombosis, intestinal ischemia from mesenteric vascular thromboses, or peripheral arterial emboli.
- Hemorrhagic complications occur in 15-35% of patients and lead to death in 6-30% of these patients.
- Peptic ulcer disease is reported to be associated with PV at a 3- to 5-fold higher rate than that of the general population. This has been attributed to increased histamine serum levels.
- Myelofibrosis and pancytopenia occur in 3-10% of patients, usually late in the disease, which is considered the spent phase of PV. In these patients, infections and bleeding complications may be the most serious health threats, and red blood cell transfusions may be required to maintain adequate red blood cell counts and to improve fatigue and other anemia-related symptoms.
- Acute leukemia or a myelodysplastic syndrome develops in 1.5% of patients treated with phlebotomy alone. The transformation risks increase to 13.5% within 5 years with treatment using chlorambucil and to 10.2% within 6-10 years in patients treated with P-32 (radioactive Phosphorus- 32). At 15 years, the transformation risk for Hydroxyurea (HU) is 5.9%, which, although not statistically significant, is a worrisome trend.

PATHOPHYSIOLOGY

Normal stem cells are present in the bone marrow of patients with PV along with abnormal clonal stem cells that interfere with or suppress normal stem cell growth and maturation. The origin of the stem cell transformation remains unknown.

Several studies suggest that a mutation on the Janus kinase-2 gene (*JAK2*) is the most likely candidate gene involved in PV pathogenesis, as *JAK2* is directly involved in the intracellular signaling following exposure to cytokines to which PV progenitor cells display hypersensitivity.

Thromboses and bleeding are frequent in persons with PV, and they result from the disruption of hemostatic mechanisms because of (1) an increased level of red blood cells and (2) an elevation of the platelet count. Tissue factor is also synthesized by blood leukocytes, the level of which is increased in persons with Myeloproliferative disorder (MPD), which can also contribute to thrombosis. Leukocyte and platelet counts were raised in 2 of the 3 patients presenting to our hospital.

Acquired von Willebrand syndrome is an established cause of bleeding in persons with PV, accounting for approximately 12-15% of all patients with this syndrome. Von Willebrand syndrome is largely related to the absorption of von Willebrand factor onto the platelets; reducing the platelet count should alleviate the bleeding and the syndrome.

Researchers believe that PV begins with one or more mutations in the DNA of a single hematopoitic stem cell, although it remains unclear exactly what initiates the disorder. Mutation in the JAK2 gene seems to be particularly important for the development of PV, as

nearly all affected individuals have a mutation in this gene. Mutations in the JAK2 and TET2 genes are associated with polycythemia vera. The function of the TET2 gene is unknown. JAK2 gene mutations result in the production of a JAK2 protein that is constantly turned on (constitutively activated), which improves the cell's ability to survive and increases production of blood cells. With so many extra cells in the bloodstream, abnormal blood clots are more likely to form. Thicker blood also flows more slowly throughout the body, which prevents organs from receiving enough oxygen. Many of the signs and symptoms of PV are related to a lack of oxygen in body tissues.

Symptoms of PV are often insidious in onset, and they are often related to blood hyperviscosity secondary to a marked increase in the cellular elements of blood, which impairs microcirculation. Symptoms include headache, dizziness, vertigo, tinnitus, visual disturbances, angina pectoris, or intermittent claudications. Bleeding complications and thrombotic complications include either profuse intraoperative hemorrhage or venous thrombosis or thromboembolism and an increased prevalence of post operative stroke and other arterial thromboses. Abdominal pain due to peptic ulcer disease is present because PV is associated with increased histamine levels and gastric acidity. Splenomegaly is also found in many patients. Pruritus may result due to increased histamine levels.

Box 1: Diagnostic criteria by the PVSG

Category A

1. Total red blood cell mass - In males, greater than or equal to 36 mL/kg; in females, greater than or equal to 32 mL/kg
2. Arterial oxygen saturation greater than or equal to 92%
3. Splenomegaly

Category B

1. Thrombocytosis with platelet count greater than 400,000/μL
2. Leukocytosis with a white blood cell count greater than 12,000/μL
3. Increased leukocyte alkaline phosphatase (ALP) greater than 100 U/L
4. Serum vitamin B-12 concentration greater than 900 pg/mL or binding capacity greater than 2200 pg/mL

The diagnosis is established with A1 plus A2 plus A3 or A1 plus A2 plus any 2 criteria from category B.

DIAGNOSIS

The Polycythemia Vera Study Group (PVSG) was the first to set rigorous criteria for the diagnosis of PV in the 1970s. With the establishment of polymerase chain reaction (PCR)-based methods for detecting the *JAK2* V617F mutation, this may become the first molecular diagnostic marker for PV. However, because of a paucity of centers doing red blood cell mass measurements, demonstrating an elevated red blood cell mass continues to become more difficult to obtain. Diagnostic criteria set by the PVSG are given in Box 1.

MANAGEMENT AND TREATMENT

Phlebotomy or bloodletting has been the mainstay of therapy for PV. The object is to remove excess cellular elements, mainly red blood cells, to improve the circulation of blood by lowering the blood viscosity. Patients with hematocrit values of more than 70% may be bled twice a week to reduce the hematocrit to the range of less than 45%. Patients with severe plethora who have altered mentation or associated vascular compromise can be bled more vigorously, with daily removal of 500 mL of whole blood. Elderly patients with some cardiovascular compromise or cerebrovascular complications should have the volume replaced with saline solution after each procedure to avoid postural hypotension. All three patients presenting to our hospital for surgery had preoperative blood hemoglobin levels in the range of 18-22 g/dL. We conducted routine preoperative phlebotomies in two of three cases excluding one surgical case in which intraoperative phlebotomy was done. Blood volume removed was replenished with normal saline or Ringers solution. Because phlebotomy is the most efficient method of lowering the hemoglobin and hematocrit levels to the reference range, all new patients should be initially phlebotomized to decrease the risk of complications.

The presence of elevated platelet counts that may be exacerbated by the phlebotomy is an indication to use myelosuppressive agents to avoid thrombotic or hemorrhagic complications. Platelet counts were elevated in two out of three of our patients preoperatively. However, follow up postoperative platelet count was not done in one patient who was phlebotomized intraoperatively, which may well have lead to post surgical fatal cerebral thrombosis of that patient.

The risks for secondary leukemia depend on the type of

therapy (e.g., phlebotomy, radioactive phosphorus-32 [^{32} P], chlorambucil) or the type of myelosuppressive agents (e.g., hydroxyurea [HU], anagrelide, interferon alfa) and duration of therapy. The PVSG demonstrated a decreased survival rate and increased mortality rate from acute leukemia in the first 5 years, and a total of 17% of patients had leukemia after 15 years with chlorambucil and with^{32} P.[4] An increased incidence of thrombotic complications occurred in the phlebotomy arm. This indicates that phlebotomy is not ideal for patients with elevated platelet counts and previous thrombosis, as are observed in patients who are older. In this situation, using HU has decreased these complications. Hydroxyurea has been the mainstay therapy for PV; it is an effective agent for myelosuppression, however, concerns have been raised regarding longterm risks for leukemic transformation. In the PVSG trial, HU therapy reduced the risk of thrombosis compared with phlebotomy alone and should be the drug of choice for patients older than 40 years.[5,11]

Anagrelide (Agrylin) is a cyclic adenosine monophosphate phosphodiesterase inhibitor that prevents platelet aggregation and inhibits megakaryocyte maturation, thereby decreasing platelet counts. Long-term treatment with anagrelide in patients with PV is efficacious and safe with respect to leukemic transformation.[6,7] To date, this agent does not appear to increase the risk of acute leukemia in patients with PV and ET over time.

Interferon alfa has been demonstrated in small anecdotal studies to possibly be useful in patients who have relapsed or progressed into AMM or with large hepatosplenomegaly. However, only low doses are tolerated and significant adverse effects from long-term use may limit its usefulness.[7]

Although HU has been considered safe for long-term maintenance, a study assessed the efficacy of low doses of aspirin (40 mg/d). Therapy with low dose aspirin in patients with thrombocytosis suppresses thromboxane biosynthesis by platelets, which is increased in PV and ET. The Italian study, European Collaboration on Low-dose Aspirin in PV(ECLAP), found aspirin efficacious for preventing thrombosis and controlling microvascular painful symptoms (erythromelalgia), which result from spontaneous platelet aggregation, in patients with polycythemia vera.[8] In a randomized control trial the use of aspirin, compared with placebo, was associated with a lower risk of fatal thrombotic events and did not increase the risk of major bleeding.[9]

Alkylating agents should not be administered to younger patients (< 40 years) who need long-term treatment. Alternative nonleukemogenic agents are needed for these patients. Women of childbearing age should only be treated with phlebotomies or interferon alfa. In young males myelosuppressive therapy can lead to aspermia, thus evaluate treatment carefully before using any chemotherapy or radiotherapy. Proven thrombotic complications warrant the use of long-term anticoagulation with warfarin.

A nationwide survey conducted in Japan to clarify the clinical features, treatment methods, and prognosis for polycythemia vera (PV) and essential thrombocythemia (ET) revealed considerable variation among Japanese hematologists.[10] These results suggest the necessity of developing treatment guidelines according to risk stratification that are suitable for individual patients.

GENERAL PRINCIPLES IN ANESTHETIC / SURGICAL MANAGEMENT

The optimum management of PV (PV) remains elusive. Patients requiring surgery are at increased risk of perioperative thrombosis and hemorrhage. A multicenter retrospective analysis was performed to estimate the frequency of thrombosis and hemorrhage after surgical procedures in patients with PV (PV) and patients with essential thrombocythemia (ET) A total of 311 surgical interventions in patients with PV and essential thrombocytopenia were analyzed. Subcutaneous heparin was administered in 54.3% cases and antiplatelet therapy in 15.4% case interventions. 74% of patients were on cytoreductive therapy before surgery. No events were observed in 83.2% procedures during 3 months of follow-up; there were 12 arterial and 12 venous thrombotic events, 23 major and 7 minor hemorrhages, and 5 deaths. Arterial thromboses were more frequent in ET (5.3% vs 1.5%; P = .08), venous events were more frequent in PV (7.7% vs 1.1%; P = .002). There was no correlation between bleeding episodes and the use of antithrombotic prophylaxis. A high proportion of PV and ET surgeries were complicated by vascular occlusion (7.7%) or by a major hemorrhage (7.3%). This study therefore emphasizes the need for prospective investigations and optimal prophylaxis in these patients.[12] Among our patients, we had one incident of post operative cerebral infarct that resulted in death of the patient.

Another study analyzing thrombosis and bleeding in PV and essential thrombocythemia; its pathogenetic

mechanisms and prevention, found that thrombotic accidents often manifest at the time of diagnosis or in the preclinical phase of the disease so that the search for a latent myeloproliferative disorder should be recommended in screenings for acquired thrombophilia, particularly when venous thromboses manifest at an unusual site.[13] Screening for high risk individuals should therefore be an imperative part of preoperative anesthesia assessment in these subjects. Hemorrhagic diathesis was found to be more rare, less ominous and mostly affected patients with very high platelet counts. In these subjects, it was found that an altered degradation and function of von Willebrand factor causes minor mucocutaneous hemorrhages, which are sometimes a prelude to major gastrointestinal bleedings. This can be a helpful warning sign during preoperative assessment of the patient, which should thus include a full physical examination. The bleeding tendency can be effectively treated by cytoreduction.

Pathogenesis and treatment of thrombotic diathesis are still controversial. In polycythemic subjects, treatment of blood hyperviscosity is essential and studies demonstrate the usefullness of low-dose aspirin in the absence of contraindications.[10] These are mostly constituted by conditions of increased bleeding risk, which, in particular, have to be evaluated when considering aspirin use in patients with PV. Future clinical research should primarily aim to assess the risk/benefit ratio of aspirin use in this disease, to better characterize the determinants of vascular risk and to reduce the high incidence of leukemias in patients with these diseases. This might require either the availability of safer cytoreductive agents or, alternatively, the use of more aggressive antiplatelet regimens in patients at high thrombotic risk. Coagulation profiles including (INR) should be done in all patients preoperatively.

In a retrospective analysis of 205 patients with primary myelofibrosis, after a median follow up of 31 months, post-diagnosis thrombosis occurred in 10.7% of patients. The majority of the events were associated with other exogenous risk factors for thrombosis such as surgery, line placement or hormonal therapy. On multivariable analysis that included age, JAK2 mutation status and leukocyte count as covariates, history of thrombosis was the only predictive variable. The study demonstrated a higher prevalence of venous, as opposed to arterial events in primary myelofibrosis, post-diagnosis, and clarifies that most venous events are mostly provoked and that prior thrombosis is the only consistently reliable predictive factor. [14]

Hypercoagulability during surgery may increase several fold in patients with PV, leading to thrombosis which according to anatomical location, may prove fatal. Prior thrombosis is a well-established risk factor for re-thrombosis in PV but scarce data are available on the rate of re-thrombosis and the optimal strategy for prevention of recurrence. A retrospectively trial estimated the rate of recurrence in a multicenter cohort of 494 patients of PV/essential thrombocythemia with previous arterial or venous thrombosis or both. Thrombosis recurred in 33.6% of patients. Sex, diagnosis (PV or essential thrombocythemia), and presence of vascular risk factors did not predict recurrence, whereas age >60 years did. Increased leukocyte count at the time of the first thrombosis was a risk factor for recurrence in patients <60 years old. Myelosuppressive therapy halved the risk in the overall cohort and the combination with antiplatelet agents or oral anticoagulants was more effective than administration of single drugs. Significant prevention of rethrombosis was independently achieved in patients with venous thromboembolism by a combination of oral anticoagulants and antiplatelet agents, and cytoreduction. It was concluded from this study that in patients with PV and essential thrombocythemia, cytoreduction protects against recurrent thrombosis. The contemporary use of oral anticoagulants after venous thromboembolism or antiplatelet agents after cerebrovascular disease or venous thromboembolism further improves the protective effect. Such findings call for prospective studies aimed at investigating whether strategies tailored according to the type of first thrombosis could improve prevention of recurrences.[15]

Therefore, therapy needs to be tailored to suit the clinical needs of the patient. However, exact diagnosis of PV should always be established preoperatively in order to rule out possible differentials responsible for erythrocytosis; all of which have known and correctable underlying causes.

Current approach to the treatment of ET should include risk stratification, choice of cytoreductive agent, and a consideration of special situations such as the perioperative patient.[16] Areas of controversy include the identification of those at high risk of complications and therapeutic decisions according to patient particular determinants like age and preoperative hematological profile. It is imperative that elective surgery be postponed until long-term control of the disease is established. This is done by normalizing red blood cell mass with regular phlebotomies (250-500 mL every alternate day) with replacement of lost blood volume with normal

saline (blood dilution), preoperatively. Patients who are elderly or cardiovascularly compromised should be phlebotomized cautiously, and smaller amounts should be removed.

Once the patient's hemoglobin and hematocrit values are reduced to within the reference range (< 45%), implement a maintenance program either by inducing iron deficiency by regular phlebotomies (frequency of the procedure depends on the rate of reaccumulation of the red blood cells) or using a myelosuppressive agent. The choice depends on the risks of secondary leukemias and the rate of thrombosis or bleeding. Patients must be cautioned not to take iron supplements. Myeloproliferative activity should be suppressed with chemotherapy tailored to patient characteristics regarding age, gender, reproductivity etc. It is essential to engage a hematologist throughout patient management to overview and guide phlebotomization through the entire perioperative period and subsequently during long term follow up of the patient. Patients with thrombotic tendencies or those who develop thrombocytosis following phlebotomy should be treated with marrow suppression.

It is advisable to maintain blood values at reference range levels by regular examination and treatment. Avoid overtreatment and toxicity by careful and judicious use of chemotherapy and radiation. Supplemental phlebotomy should always be preferred over excess marrow suppression. Prolonged fasting without adequate replacement should be avoided because this can lead to dangerously high hematocrit levels in patients already predisposed to hypercoagulability. Even fasting for no longer than 4-6 hrs should always be accompanied by ample pre operative hydration. Intraoperatively the patients' baseline hypercoagulability increases by a hundred fold. Aggressive hydration should thus continue throughout the surgical period and adequate urine output must be ensured. Emergent surgery may require intraoperative phlebotomies. This must be done with extreme caution taking care to replace lost volume and avoiding vasoconstriction from volume depletion that can risk multiorgan ischemia or intraoperative thrombus formation. Central venous monitoring is recommended in all patients to monitor not only fluid status but also for the provision of a large gauge central venous line for rapid infusion rates that may be required in such patients. Monitoring of vitals and clinical evaluation of the patient for possibility of stroke or hemorrhage should continue from the intraoperative through the postoperative period.

All patients with PV presenting for surgery; elective or emergent, should be admitted to the intensive care unit in the immediate post op period for at least a period of forty eight hours with strict vitals observation and concurrent clinical and laboratory evaluation. Early ambulation and aggressive use of analgesics preferably opioids is recommended to prevent stasis of blood flow and discourage formation of deep venous thrombosis to which these patients are at increased risk. Compression stockings to avoid clot formation and use of peripheral local anesthetic blocks to relieve postoperative pain and thus allow early ambulation should be undertaken in these patients.

CONCLUSIONS

Patients with PV are at increased risk of perioperative thrombosis and hemorrhage. Postoperative follow-up may be complicated by pulmonary or cerebral thrombosis/ embolisms or hemorrhage. We conclude that PV is a risk factor for thromboembolic events that requires meticulous attention to perioperative assessment of patient blood profile and subsequently tailored treatment strategies in order to avoid substantial morbidity and mortality.

REFERENCES

1. Passamonti F, Malabarba L, Orlandi E, et al.(2003). Polycythemia vera in young patients: a study on the long-term risk of thrombosis, myelofibrosis and leukemia. Haematologica 88 (1): 13–8.
2. Berlin NI (1975). Diagnosis and classification of polycythemia. Semin Hematol 12: 339.
3. Anía B, Suman V, Sobell J (1994). Trends in the incidence of polycythemia vera among Olmsted County, Minnesota residents, 1935-1989". Am J Hematol 47 (2): 89–93.
4 Ruggeri M, Rodeghiero F, Tosetto A. Post surgery outcomes in patients with polycythemia vera and essential thrombocythemia: a retrospective survey. Blood 2008 Jan 15;111(2):666-71.
5. Weinfeld A, Swolin B, Westin J. Acute leukaemia after hydroxyurea therapy in polycythaemia vera and allied disorders: prospective study of efficacy and leukaemogenicity with therapeutic implications. Eur J Haematol 1994;52(3):134-9.
6. Fruchtman SM, Pettit RM, Gilbert HS, et al, and

the Anagrelide Study Group. Anagrelide: analysis of long-term safety and leukemogenic potential in myeloproliferative diseases (MPDs) [abstract]. Blood 2002;100:70a.

7. Fruchtman SM, Petitt RM, Gilbert HS, Fiddler G, Lyne A, and the Anagrelide Study Group Leukemia Research. Anagrelide: analysis of long-term efficacy, safety and leukemogenic potential in myeloproliferative disorders. Leuk Res. 2005;29(5):481-91.
8. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004;350(2):114-24.
9. Squizzato A, Romualdi E, Middeldorp S. Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. Cochrane database sys rev. 2008 Apr 16;(2):CD006503.
10. Dan K, Yamada T, Kimura Y Clinical features of polycythemia vera and essential thrombocythemia in Japan: retrospective analysis of a nationwide survey by the Japanese Elderly Leukemia and Lymphoma Study Group. Int J Heamatol 2006;83(5):443-9.
11. Fruchtman SM, Mack K, Kaplan ME, et al. From efficacy to safety: a Polycythemia Vera Study Group report on hydroxyurea in patients with polycythemia vera. Semin Hematol 1997;34(1):17-23.
12. Berk PD, Goldberg JD, Donovan PB, et al. Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. Semin Hematol 1986;23(2):132-43.
13. Landolfi R, Cipriani MC, Novarese L. Thrombosis and bleeding in polycythemia vera and essential thrombocythemia: pathogenetic mechanisms and prevention. Best pract clin res heamatol. 2006;19(3):617-33.
14. Elliott MA, Pardanani A, Lasho TL. Thrombosis in myelofibrosis: prior thrombosis is the only predictive factor and most venous events are provoked. Heamatologica 2010;95(10):1788-91.
15. De Stefano V, Za T, Rossi E. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Heamatologica 2008;93(3):372-80.
16. Beer PA, Erber WN, Campbell PJ. How I treat essential thrombocythemia. Blood 2011;117(5):1472-82.