



Treatment of polycythemia vera

TIZIANO BARBUI, GUIDO FINAZZI

Department of Hematology, Ospedali Riuniti, Bergamo, Italy

Abstract

Background and Objective. Current guidelines for the management of patients with polycythemia vera (PV) derive from a few clinical trials and several uncontrolled clinical studies. The purpose of this paper is to critically review the available evidence in literature for selecting the best treatment in the single patient.

Methods. The authors have been working in this field contributing original papers whose data have been used for this study. In addition, the material analyzed in this article includes papers published in the journals covered by the Science Citation Index® and Medline®.

Results. Therapeutic strategies for patients with PV include both cytoreductive and antithrombotic drugs. Among cytoreductive treatments, phlebotomy is associated with poor compliance and an increased incidence of thrombosis in the first three-five years, whereas chemotherapy may induce a higher risk of secondary malignancies after seven-ten years of follow-up. New cytoreductive drugs virtually devoid of mutagenic risk include α -interferon and anagrelide, but their role in reducing thrombotic complications or mortality remains to be demonstrated. Antithrombotic drugs, such as aspirin, are frequently used in PV, despite doubts regarding safety and efficacy.

Conclusions. The management of patients with PV is a difficult balance between the prevention of thrombotic complications and the risk of drug side effects and toxicity. Appropriate studies are needed and an European collaboration has been set up for launching a randomized, placebo-controlled clinical trial (*European Collaboration on Low-Dose Aspirin - ECLAP study*) aimed at testing the efficacy of low-dose aspirin in preventing thrombosis and prolonging survival in PV patients.

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Key words: polycythemia vera, myeloproliferative disorders, clinical trials

Polycythemia vera is a clonal disorder of the hematopoietic stem cell compartment arising in response to not yet identified stimuli. This results in an increased sensitivity of the bone marrow cells to normally produced regulatory factors

and, consequently, to an overproduction of circulating red blood cells, leukocytes and platelets.^{1,2}

The chronic course of this myeloproliferative disorder slowly progresses into subsequent clinical and hematological phases. The onset might be insidious and symptoms precede an overt diagnosis of PV by years. During this *developmental phase*, patients may be asymptomatic or suffer from severe complications. Recently, the *Gruppo Italiano Studio Policitemia* (GISP) has shown that 14% of patients had thrombosis before diagnosis of PV and 20% had a thrombotic event as the presenting symptom of disease.³ Cerebral ischemia accounted for 70% of arterial thromboses at diagnosis and was as prevalent as myocardial infarction (30%) before diagnosis of PV.³ The *polycythemic phase*, clearly defined by the current diagnostic criteria,^{4,5} may be either asymptomatic or characterized by thrombotic events of different severity, also depending on the concomitant presence of other risk factors for vascular disease. Bleeding complications are less frequent than thrombosis and account for 15-30% of cases. The *spent phase* is the final stage, characterized by anemia, leukopenia, thrombocytopenia and by a leuko-erythroblastic peripheral blood picture. This transformation can be registered in up to 20% of PV patients, after an average interval of 10 years from diagnosis and the outcome is very poor since no effective treatment is available. Recently, a small series of seven patients with transformed PV underwent allogeneic bone marrow transplant and the results seem promising.⁶

Current treatments of PV have dramatically improved the survival of patients in the pre-transformed stages of this myeloproliferative disorder.⁷ In fact, the median life expectancy in untreated PV patients varies from 6 to 18 months from diagnosis; in contrast, by controlling the vascular complications with cytoreduction and antithrombotic drugs, median survival exceeds 10 years.⁸ Unfortunately, we have to face with complications chiefly bound to the cytotoxic therapy that are one of the leading cause of death of these patients.⁹ In this paper, we briefly present the results of clinical trials of PV therapy, the accumulating experience with new drugs and the proposals for some clinical studies.

Correspondence: Prof. Tiziano Barbui, Hematology Department, Ospedali Riuniti, largo Barozzi 1, 24100 Bergamo, Italy. Phone international +39-35-269490 • Fax: international +39-35-269667 • E-mail: ematologia@cyberg.it

Therapeutic options in PV

Available information for therapeutic recommendations in PV derives from: a) a very limited number of randomized clinical trials;^{4,10-12} b) a series of prospective and retrospective studies which described the natural history of PV patients and indirectly evaluated the role of the different strategies on the main outcomes of the disease (reviewed in ref. #13). It can be useful to distinguish between treatments given to reduce red blood cell mass and myeloid hyperplasia ('cytoreductive' therapy) from those aimed exclusively at preventing thrombotic complications ('antithrombotic' therapy).

Cytoreduction

The most influential study on the treatment of PV was initiated by the *Polycythemia Vera Study Group* more than twenty years ago (01 trial).⁴ Between 1967 and 1974, 431 evaluable patients were randomized to one of the following treatments: a) phlebotomy alone; b) ³²P plus phlebotomy and c) chlorambucil plus phlebotomy. The results of this trial and recent analysis on the long-term outcome of the patients originally enrolled in the study¹⁴ provided useful information on the role of phlebotomy and the value of *old* myelosuppressive agents in the management of PV.

Phlebotomy

Patients randomized to the phlebotomy arm of the PVSG-01 study showed a very high incidence of thrombosis particularly in the first three years of treatment. Thrombosis was most common in those with a high phlebotomy rate, previous thrombotic events or advanced age. A number of factors might have played a role in the high thrombosis rate. These are the uncontrolled thrombocytopenia and the fact that over the first few years of the study the target hematocrit marking adequate treatment was below 0.52 and this was subsequently reduced to less than 0.45 when further key evidence on the influence of hematocrit on blood flow and thrombosis was produced.¹⁵

Following the initial three years of increased thrombotic risk in the phlebotomy-only arm, the thrombotic rate in all three arms was found to be the same. On the other hand, after 3-5 years of study, patients treated with ³²P or chlorambucil began to develop an excess incidence of acute leukemia, lymphoma and carcinomas of the gastrointestinal tract and skin as compared to those treated with phlebotomy alone. For this reason, patients treated in the phlebotomy arm of the PVSG-01 trial had an overall better median survival at 12.6 years than the other two arms (chlorambucil 9.1 years, P32 10.9 years).

However, this has to be interpreted with caution in the light of the results of long-term follow-up studies. Najean *et al.*¹⁴ reported that of the 104

patients entered by their group into the phlebotomy arm of PVSG-01 and the later PVSG-05¹¹ study, more than 50% were excluded from this treatment arm by the 5th year and 90% by the 10th year. This was due to the necessity of introducing some forms of cytoreductive therapy for age, risk of vascular accidents and excess platelet number. Other reasons were the patient's poor compliance to phlebotomy, the development of splenomegaly with signs of spent phase or myelofibrosis.

The large withdrawal of patients from the phlebotomy arm is considered to play a role in the reported incidence of acute leukemic transformation in this group of patients.⁷ This is quoted to be 1.5% and reflects the natural incidence of leukemia in PV in patients not receiving any cytoreductive therapy. However, this figure relates to a selected group of patients with a less proliferative form of PV, which probably has a lower incidence of leukemic transformation in its natural history.

Long-term follow-up observation also raised concern about an increased incidence of myelofibrosis in PV patients treated with phlebotomy alone. In one study,¹⁴ the actuarial risk of developing the spent phase of the disease or a myelofibrosis with myeloid metaplasia of the spleen was much higher in patients who continued to be treated by phlebotomies alone. When phlebotomized patients subsequently received myelosuppression, the risk of progression to myelofibrosis was similar to that observed in subjects treated by ³²P from the start. Similar findings were also reported by others,¹⁶ but were not confirmed by the PVSG.¹⁷

Radio-active phosphorus (³²P)

³²P has been used in the treatment of PV for over 50 years with remarkable myelosuppressive efficacy. Complete remission was obtained in up to 98% of cases after a single injection of 2.8 to 3.5 mCi/m².¹⁴ Sometimes, a further two doses may be required at 3-6 months interval.

The drug is usually well tolerated and allows longstanding hematological remission with excellent quality of life. The control of hematocrit and platelet count provided by ³²P leads to a low incidence of thrombotic complications compared with phlebotomy alone.⁴ However, ³²P was found to be responsible of an increased incidence of hematological and non-hematological malignancies in the PVSG-01 trial⁴ and in other studies.¹⁴ The frequency of acute leukemias and myelodysplastic syndromes in PV patients treated with ³²P is dose-related and increases regularly from the 5th year onward.¹⁴ This latter observation may explain the lower incidence of acute leukemic transformation with the use of ³²P in series of PV patients who were examined after a shorter follow-up period.^{10,18} Weighing the current evidence of effectiveness and side effects of ³²P, its current place is restricted to patients over the

age of 70 years, particularly those with poor venous access or unable to attend regularly for medical care.⁷

Alkylating agents

Chlorambucil was used in one of the three arms of the PVSG-01 study. In 1981, the group reported that treatment with this drug was associated with a statistically significant increased risk of developing acute leukemia.¹⁹ At the time of that report, 18 cases of acute leukemia had been observed on the chlorambucil arm of the study, 1 on the phlebotomy arm and 9 among patients receiving ³²P. Therefore, the PVSG recommended that treatment with chlorambucil had to be stopped. This recommendation was then extended to all alkylating agents in the treatment of PV, although the incidence of acute leukemias seen in other studies with busulphan¹⁰ or pipobroman²⁰ was much lower.

In conclusion, the PVSG 01 study raised a therapeutic dilemma that remains still unresolved: balancing the risk of thrombosis (and perhaps myelofibrosis) of phlebotomy with that of neoplastic transformation induced by ³²P and alkylating agents. Consequently, in the late seventies, the search for a nonmutagenic myelosuppressive agent led the PVSG to investigate hydroxyurea.

Hydroxyurea

HU is a potent nonalkylating agent that inhibits the synthesis of DNA by inhibiting the enzyme ribonucleoside reductase. Because of its mechanism of action, it was hoped that this drug would prove effective and safe for long term use in PV patients. In 1977, the PVSG initiated a phase II, non randomized study (protocol 08) aimed at establishing the short efficacy of the drug.²¹ The results indicated that hydroxyurea was able to decrease the incidence of life-threatening thrombosis as compared with historical phlebotomized patients (13.7% vs. 38.1%) with a low prevalence of acute leukemia occurring during the first 378 weeks of study (2 patients out of 51, 3.9%).

Unfortunately, restrictions in funding hampered the PVSG's ability to proceed with further randomized trials. Instead, the decision was made to maintain patients already enrolled in the 08-protocol on HU in order to establish its long-term safety. The PVSG's experience was recently updated.^{9,22} The 51 patients originally included in the 08-study have been followed for medium and maximum of 9.6 and 15.3 years respectively. The incidence of acute leukemia, spent phase of myeloid metaplasia, and death were compared with the incidence in patients treated only with phlebotomy in the initial protocol (PVSG-01). Five leukemias were observed in the HU group (9.8%) but there were no statistically significant differences in the incidence of any of the three end-points in comparison with the phlebotomy-

arm group (Table 1).

Other studies have investigated the long-term safety of HU.^{23,24} The incidence of acute leukemia in nearly 200 patients treated exclusively with HU was about 5-10% over approximately 10 years and there are now at least 46 patients with MPD in the literature who have developed acute leukemia after treatment only with HU. Thus, some anxiety remains about the leukemogenic potential of this drug and this prompted to evaluate other agents thought to be less toxic, such as interferon or anagrelide.

Interferon

Recombinant interferon- α (IFN) was found to be active in PV with an antiproliferative activity virtually devoid of mutagenic risk.²⁵ IFN has been evaluated in some phase II studies and overall results indicate that red cell mass can be controlled within 6 to 12 months in up to 70% of cases, as seen by the reduction of the need for phlebotomy. In addition, IFN can reverse the associated splenomegaly, leucocytosis and thrombocytosis in the majority of patients and it is particularly effective for the treatment of generalized pruritus.^{26,27}

These clinical findings are supported by *in vitro* studies showing a significant and progressive reduction of circulating CFU-GM and BFU-E during the first two months of therapy in most patients.²⁸ In addition, IFN inhibits megakaryopoiesis and antagonizes the action of platelet-derived growth factor (PDGF), a product of megakaryocytes which initiates fibroblast proliferation.²⁹ This observation suggests that IFN could, theoretically, modify polycythemia's natural history and reduce or delay the development of myelofibrosis. Hematological responses have been seen in 50% of patients with idiopathic myelofibrosis, usually those with a hyperproliferative type of disease.¹ Side effects of this drug are a significant problem, causing therapy withdrawal in approximately a third of patients. Signs of chronic IFN toxicity include weakness, myalgia, weight and hair loss, severe depression and gastrointestinal and cardiovascular toxicity.^{26,27}

Table 1. Events in patients with polycythemia vera in the first 15.3 years of study by the Polycythemia Vera Study Group.

	Hydroxyurea (%)	Phlebotomy (%)
Total patients	51	134
Acute leukemia	5 (9.8)	5 (3.7)
Spent phase	4 (7.8)	17 (12.7)
Death	20 (39.2)	74 (55.2)

All the differences are not significant (see ref. #9).

Thus, IFN seems to be a promising agent in cytoreductive treatment of PV, especially in younger patients and in those with burdensome organomegaly. Long-term studies are however required to establish its effect on relevant clinical end-points, such as prevention of thrombosis, myelofibrosis, leukemic transformation and, of course, survival.

Anagrelide

Another drug for which a leukemogenic effect would not be anticipated is anagrelide, a member of imidazo(2,1-b)quinazolin-2-one series of compounds.³⁰ The drug, given orally alone or in combination with HU, has been found to be extremely efficacious in controlling thrombocytopenia in patients with PV and other myeloproliferative disorders (MPD). The mechanism whereby anagrelide reduces platelet count, without affecting leukocytes and red blood cells, is not yet completely understood, but there are data showing that its major action is the inhibition of megakaryocyte maturation.³¹ No chromosomal damages have been reported related to its use. Importantly, life-threatening vascular symptoms dropped to 22% within the first three months of treatment and this renders the drug of great utility for thrombocytopenic states complicating PV. However, adverse reactions, including headache, fluid retention, nausea, diarrhea and abdominal pain, have been reported and in older people anagrelide may precipitate congestive heart failure.^{30,31} Since the available information regarding anagrelide treatment comes from phase II studies, comparative clinical trials are urgently necessary to define a role of this interesting drug in the strategy of PV treatment.

Antithrombotic therapy

The use of aspirin or other antiplatelet agents in patients with PV and other myeloproliferative disorders remains controversial.³² Laboratory tests of platelet function (e.g. bleeding time, platelet aggregation studies) have been generally unreliable in predicting the risk of bleeding and thrombosis.³³ Therefore, the decision to use aspirin must be based primarily on the clinical picture. Aspirin may be useful in PV patients who have recurrent thrombotic complications, particularly those with digital or cerebrovascular occlusive syndromes.^{34,35} On the other hand, patients with prior histories of bleeding problems, particularly of the gastrointestinal tract, may be at risk of serious bleeding with aspirin use. The relative benefits and risks of aspirin in patients without a clear-cut prior history of bleeding or thrombosis are not established.

In a single, small clinical trial, the PVSG randomized 163 PV subjects to be treated with ³²P or phlebotomy associated with aspirin 900 mg/d plus dipyridamole.¹¹ After a median follow-up of 1.6 years, 6 bleeding episodes, mostly gastrointestinal,

and 7 thrombotic events were observed in the group assigned to antiplatelet therapy while 2 thrombotic episodes and no bleeding were observed in the other group. On this basis the study was discontinued and the authors concluded that antiplatelet agents were both ineffective and potentially dangerous in PV patients. However, neither the excess of thrombosis nor that of bleeding was statistically significant, due to the low number of subjects recruited in the trial, and both the play of chance or even a moderate imbalance between groups could be responsible for such results. In addition, the excess of gastrointestinal bleeding was most likely related to the high dose of aspirin used in that study.

Lower aspirin doses (30-250 mg/day) are at least as effective as higher doses and are better tolerated, as shown by recent clinical trials in patients with vascular disease.^{36,37} Therefore, the efficacy and safety of low-dose aspirin in preventing thrombosis in patients with PV remains to be tested in a properly designed clinical trial. In order to create a favorable scenario for organising a prospective evaluation of low-dose aspirin in PV patients, the *Gruppo Italiano Studio Policitemia* has recently completed two preliminary studies.

First, a retrospective analysis of 1213 patients followed over twenty years was set up to estimate the sample size of the clinical trial.³ The incidence of thrombosis during follow-up was 3.4%/year, with evidence of higher risk in patients with advanced age and/or previous thrombosis. Overall death was 2.94 per 100 patients/year, that is 70% higher than expected in the general Italian population. The most prevalent causes of death were: thrombosis (29%), acute leukemia (15%) and other malignancies (15%).

Second, the GISP carried out a pilot study on the safety of low-dose aspirin (40 mg/day) in PV patients.¹² One hundred and twelve patients, without clear indications (e.g. previous arterial thrombosis) or contraindications (e.g. gastrointestinal bleeding) to aspirin, have been randomized to low-dose aspirin or placebo and follow-up more than 12 months. No difference in side effects or adverse events were apparent, showing that a large scale evaluation of low-dose aspirin in PV patients is feasible.¹³

Polycythemia and hyperhomocysteinemia are risk factors for thrombosis. Since red blood cells actively metabolize methionine to homocysteine, Tonon *et al.*³⁸ have recently investigated whether or not patients with polycythemia have increased plasma levels of homocysteine, which might contribute to their increased thrombotic risk. This study excluded that high plasma homocysteine levels contribute to the increased thrombotic risk of polycythemic patients.

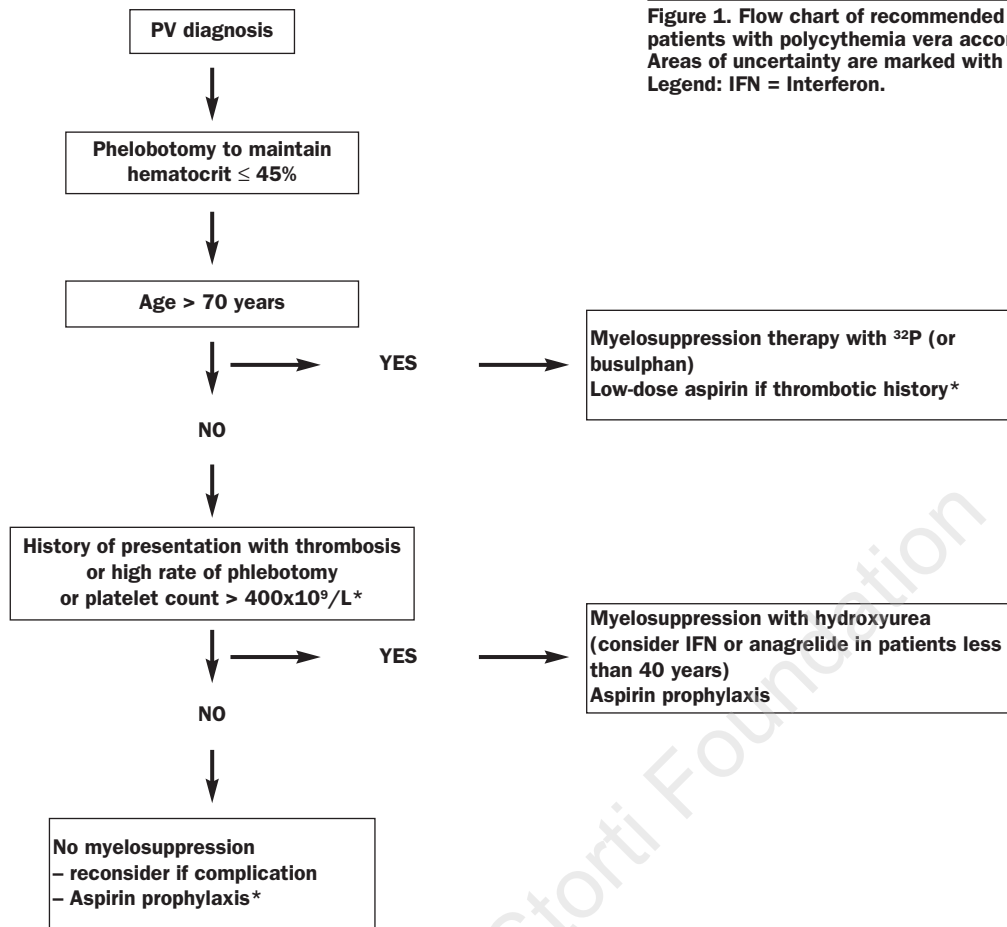


Figure 1. Flow chart of recommended treatment for patients with polycythemia vera according to risk factors. Areas of uncertainty are marked with an asterisk. Legend: IFN = Interferon.

Current therapeutic recommendations and future directions

Recommendations about the care of an individual patient should derive from an integration of the best available evidence in literature with clinical experience and practice. As briefly reviewed above, a sound scientific basis for making therapeutic decisions in PV patients is lacking, due to the paucity of randomized clinical trials.

Concern about long-term leukemogenicity of cytotoxic treatments suggests to differentiate treatment primarily by age (Figure 1). In patients less than 50 years old, phlebotomy alone should be considered the treatment of choice, with the goal to maintain the hematocrit to less than 46%. In patients over 70 years old, myelosuppressive therapy is indicated, and ^{32}P is probably the best therapeutic option. In patients between the ages of 50 and 70, there is room for individualization. The administration of hydroxyurea seems justified in case of frequent phlebotomies or previous thrombotic events. In all patients, the association of low-dose aspirin should be considered in case of cerebrovascular,

coronary or peripheral arterial ischemia. Warfarin should be preferred in patients with recurrent venous thrombosis. However, these recommendations should be taken with caution on the light of a series of relevant considerations.

First, there are methodological limits of the PVSG-01 trial, that represents the cornerstone of the above recommendations. For instance, it has been outlined that 69 patients out of 156 died in the ^{32}P group (44%) and 43 patients out of 132 (32%) died in the group allocated to phlebotomy. Although not statistically significant, this 28% relative reduction of mortality is not trivial and one can wonder whether phlebotomy prolongs survival in comparison to myelosuppression and whether the trial had the statistical power necessary to detect this potential advantage.¹³

Second, the major problem with phlebotomy is the long-term feasibility of this procedure. As discussed earlier, this observation weakens the conclusions reached in the phlebotomy arm of the PVSG 01 study.

Third, despite concerns about their potential leu-

kemogenicity, hydroxyurea remains the myelosuppressive drug of choice in younger patients. Unfortunately, at the moment, no other drugs have shown convincing evidence of efficacy on hard clinical end-points, such as major thrombosis or survival. Clinical trials are required to assess the role of IFN or anagrelide in patients who are more likely to be exposed for long period to cytoreductive drugs, such as younger individuals, or in those who become resistant to HU or pipobroman.

Finally, a scientific answer regarding the effectiveness and safety of low-dose aspirin in PV is expected from a large scale, placebo-controlled clinical trial currently being organized (*European Collaboration on Low-Dose Aspirin – ECLAP Study*) and funded by the European Union. Until the trial is completed, we recommend to use aspirin in microvascular disturbances of PV, such as erythromelalgia, and in patients with a history of arterial thrombosis. This drug should be avoided when a clear history of bleeding has been documented.

In conclusion, randomized clinical trials aimed at producing scientific evidence on the benefit/risk profile of therapeutic modalities are mandatory but difficult to be done in a rare disease such as PV. The end-points of such studies should be clinically relevant and patients should be followed at least for 3-5 years if the main outcome is the reduction of thrombotic events and 5-10 years if the goal is to assess the rate of malignancies. Only international collaborations can recruit rapidly and follow an adequate number of cases for these purposes. The European network set up for the low-dose aspirin clinical trial represents an important step forward towards this important goal.

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The two authors equally contributed to the analysis of the literature and writing of the paper.

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Manuscript processing

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