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REVIEW ARTICLE

Treatment of Polycythemia Vera: A Clinical Oncology Perspective

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ABSTRACT

Polycythemia vera is a clonal myeloproliferative disorder. The Polycythemia Vera Study Group was established in 1967; its earliest accomplishment was to create a set of diagnostic criteria for polycythemia vera that have since proven their value. The Polycythemia Vera Study Group then spent almost 30 years conducting sophisticated clinical trials documenting a variety of therapeutic approaches for polycythemia vera, principally phlebotomy alone, or myelosuppression [with either radiophosphorus, an alkylating agent (chlorambucil), or hydroxyurea] combined with supplemental phlebotomy. With current management, survival of patients with polycythemia vera improves dramatically compared with historical controls treated with phlebotomy alone. Today, most clinicians will treat younger patients with polycythemia vera with hydroxyurea. The drawbacks are that this drug has to be taken regularly and the patient must scrupulously adhere to the schedule. For elderly patients with polycythemia vera, management by phlebotomy alone carries a high risk of early thrombosis; radiophosphorus remains the treatment of choice for these patients.

Key Words: *Phlebotomy, Polycythemia vera, Radiophosphorus, Treatment*

INTRODUCTION

Polycythemia vera (PV) was first reported by Vaquez in 1892[1] before being defined more clearly by Osler in 1903.[2] It is a clonal, progressive myeloproliferative disorder (MPD), characterised by excessive erythropoiesis accompanied by low serum erythropoietin levels. The most readily accepted theory of the origins of this disease is that the malignant erythroid progenitor cells in the bone marrow are exquisitely sensitive to erythropoietin.[3]

PV tends to occur most commonly in the sixth and seventh decades of life. Certain ethnic and racial groups are more predisposed, e.g. the incidence in Jewish people (where 5% of patients present before the age of 40 years) is four-fold higher than in other populations. The common signs and symptoms of PV are shown in Table 1. Thrombo-haemorrhagic complications are frequently encountered in patients with PV (Table 2); these complications usually correlate with the haematocrit (Hct) level.

Table 1. Common signs and symptoms of polycythemia vera

Clinical feature	Patients with signs/symptoms (%)
Headache	41-48
Dyspnoea	23-34
Weakness	35-47
Plethora	65-84
Dizziness	25-43
Visual changes	19-31
GI discomfort	23-50
Haematemesis	2-6
Angina	16-23
Pruritus	14-40
Splenomegaly	50-80
Hepatomegaly	30-50

Abbreviation: GI = gastrointestinal.

Table 2. Incidence of thrombo-haemorrhagic complications in polycythemia vera

Complication	Patients with complication (%)
Any thrombosis	20-60
Any haemorrhage	5-35
Cerebral thrombosis	6-18
Coronary thrombosis	3-11
PVD	6-20
DVT	7-13
Budd-Chiari syndrome	1-8
Cardiac valve abnormalities	80
Cerebral haemorrhage	6-10
PUD	8-20
Upper GI bleeding	3-10

Abbreviations: PVD = peripheral vascular disease; DVT = deep venous thrombosis; PUD = peptic ulcer disease.

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The Polycythemia Vera Study Group (PVSG), an international study group initiated in 1967, developed a series of widely available and recognised diagnostic criteria (Table 3). With current management, the median survival of a patient can exceed 10 years. This contrasts with those left untreated, 50% of whom die within 18 months of the onset of symptoms, mainly from thrombosis.[4]

CURRENT TREATMENT METHODS

The purpose of initiating treatment in PV is to decrease the Hct level to less than 45% and thereby prevent thrombo-haemorrhagic complications.[5] Treatment methods currently in use include phlebotomy, radiophosphorus (^{32}P), and chemotherapy.

Phlebotomy (Venesection)

Phlebotomy offers prompt and effective restoration of the red cell mass and blood volume to normal values. It is used primarily to provide immediate relief of symptoms, especially vertigo, fullness in the head, headache, and tinnitus. Normally, 300-500 mLs of blood are removed repeatedly at 1- to 3-day intervals. Using this technique, it is possible to produce a remission lasting for several months.

However, phlebotomy does not suppress the basis of the MPD, nor does it control the leukocytosis and thrombocytosis. It may also adversely affect the cardiovascular system in the elderly. Besides, certain complications [of phlebotomy] are well documented, including progressive and sometimes extreme thrombocytosis, and chronic iron deficiency symptoms, e.g. pica, angular stomatitis, and glossitis. In addition, progressive splenomegaly or pruritus not controllable by antihistamines may persist despite Hct control by phlebotomy. When phlebotomy is required more often than bimonthly, most clinicians prefer to use other forms of therapy.

Radiophosphorus

^{32}P was first introduced by Lawrence for the treatment of PV in 1939.[6] ^{32}P is a pure β-emitter (maximum energy 1.71 MeV), with a mean range in tissue of 3 mm. Its half-life is 14.3 days. Usually, it is given in the form of an intravenous bolus injection. As recommended by the American College of Radiology, the dosage may be standard [3.0 mCi (111 MBq)] or based on body surface area [2.3 mCi/m^2 (85 MBq/m^2)], but should not exceed 5.0 mCi (185 MBq) for each injection. Any relapse or failure to respond within 12 weeks may require retreatment with dosages up to 7.0 mCi (260 MBq).[7]

After intravenous administration, ^{32}P is preferentially taken up by bone, spleen, and liver. It is then selectively concentrated in mitotically-active cells in bone marrow, before being incorporated in calcium phosphate of bone. The effective dose of ^{32}P for adults is given by the International Commission of Radiological Protection (ICRP) as 2.4 mSv/MBq, with the absorbed dose to bone marrow as 11 mGy/MBq.[8] These calculations are based on the metabolic model from ICRP Publication 53,[9] which assumes that 30% of the injected activity goes to mineral bone to be permanently retained, and 70% is distributed in soft tissue. In 1948, 9 years after ^{32}P was first employed to treat PV, Hall reported the occurrence of acute leukemia following the use of this isotope.[10]

Chemotherapy

Chemotherapeutic agents commonly used include chlorambucil, hydroxyurea, and busulfan. The myelosuppressive effect of these agents is an important component in the treatment of PV. The aim is to control the peripheral blood counts, thereby minimising potential complications arising from elevated circulating elements.[11] Their role, including efficacy and side effects, has been extensively investigated by the Polycythemia Vera Study Group.

POLYCYTHEMIA VERA STUDY GROUP

The PVSG was an international study group set up by Louis R Wasserman and Nathaniel Berlin in 1967. Supported by the National Cancer Institute (NCI), the group conducted several, prospective, randomised, controlled clinical trials aimed at identifying the best modality for treating PV. Notable among these were PVSG-01, PVSG-05, and PVSG-08. As part of the same project, the PVSG developed criteria for the diagnosis of this disease (Table 3).[12]

PVSG-01 Study

The aim of this initial study was to test whether phlebotomy alone was as effective as myelosuppressive therapy supp lemented with phlebotomy. Between 1967 and 1974, 431 eligible patients were registered and randomised to one of three treatment options (Figure 1):

- phlebotomy alone
- ^{32}P with supplemental phlebotomy as needed
- chlorambucil with supplemental phlebotomy.

In each case, phlebotomy was performed to maintain the Hct at less than 40% to 45%. The minimum follow-up

Table 3. Diagnostic criteria for entry into the first Polycythemia Vera Study Group trial (PVSG-01)*

Category A		Category B	
A1	Increased total red cell volume Male ≥ 36 mL/kg Female ≥ 32 mL/kg	B1	Thrombocytosis (platelet count > 400,000 /mL)
A2	Normal arterial oxygen saturation (≥ 92%)	B2	Leukocytosis > 12,000 /mL (no fever or infection)
A3	Splenomegaly	B3	Increased leukocyte alkaline phosphatase (> 100)
		B4	Serum B_{12} > 900 pg/mL or unbound B_{12} binding capacity > 0.22 pg/mL

*Diagnosis of polycythemia vera virtually certain in the presence of A1 + A2 + A3 or A1 + A2 + any two from category B

period for surviving patients was 11 years. The results of this study can be summarised in terms of three major outcomes — namely, overall survival, incidence of thrombosis, and malignant complications.

Overall Survival

Overall survival was found to be equivalent in the phlebotomy-alone and ^{32}P/phlebotomy groups, although there was a decrease in survival in the chlorambucil/phlebotomy group that was not apparent until the first 7 years after randomisation (Figure 2). The median survival times were 13.9 years with phlebotomy alone, 11.8 years with ^{32}P/phlebotomy, and 8.9 years with chlorambucil/phlebotomy. Differences in overall survival among the three treatment arms were principally the result of differences in the incidence of fatal events late in the study. Indeed, during the first 7 years of the study, overall survival was equivalent in the three treatment groups. The causes of death, however, were different:

- thrombosis occurred predominantly among phlebotomy-treated patients, especially during the first 4 years of the study
- leukaemia and cancer occurred predominantly in patients with myelosuppression, particularly after the 4th year of the study. This reflected a progressive and increasing incidence of malignant complications in patients receiving myelosuppressive regimens
- a disproportionately large number of thrombotic deaths occurred in patients in the phlebotomy-alone group, particularly during the first 4 years of the study. This contrasted with a disproportionately large proportion of deaths from cancer and leukaemia in patients in the two myelosuppressive groups beyond the 5th year. Thus, although there were no significant differences in survival during the first 7 years of the study, the causes of death were markedly influenced by the therapy.

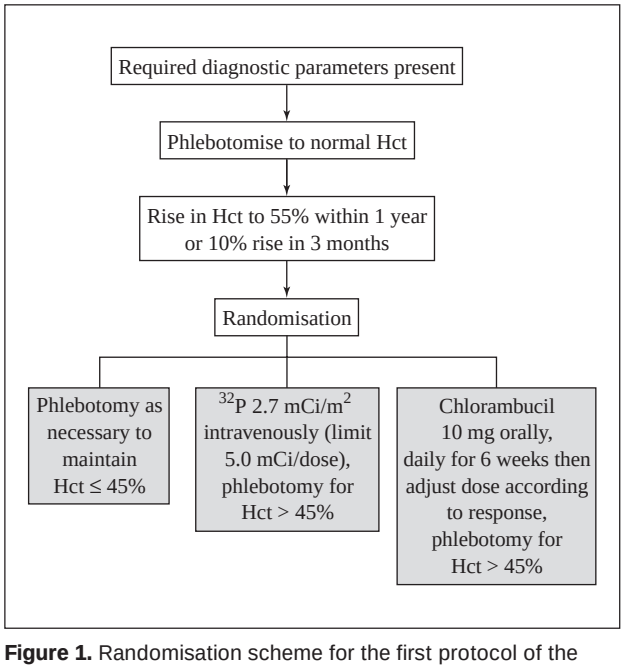

Figure 1. Randomisation scheme for the first protocol of the PVSG (PVSG-01 study).

Thrombosis

The most common complication due to thrombosis was cerebrovascular accident, accounting for about

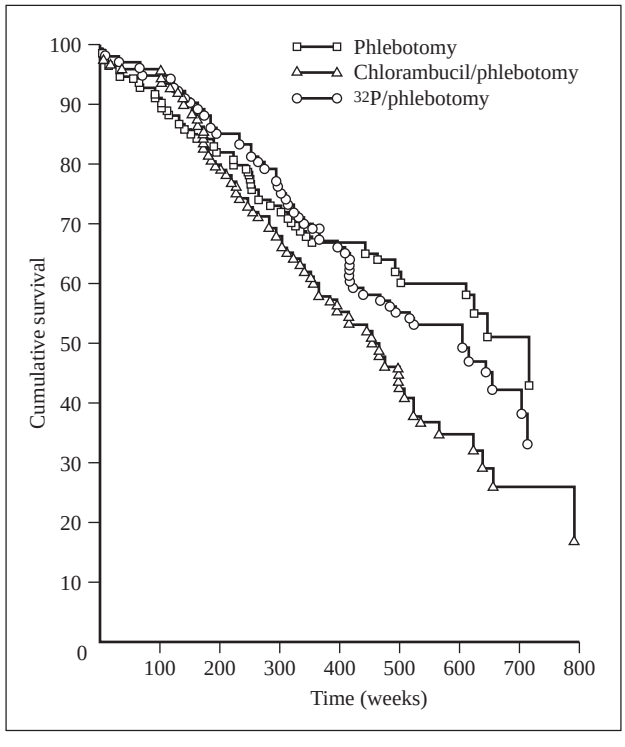

Figure 2. Cumulative survival of patients in the three treatment arms of PVSG-01. Reprinted with permission.[11]

one third of the thrombotic events. Other events included myocardial infarction, peripheral arterial occlusion, and pulmonary infarctions.

During the first 5 to 7 years of the study, patients in the phlebotomy-alone group had significantly poorer (i.e. shorter) thrombosis-free cumulative survival times compared with patients in the two myelosuppression groups. Several thrombosis-related risk factors were identified by multivariate analysis, including treatment with phlebotomy, a history of prior thrombosis, and advanced age.

Malignancies

The incidences of haematological malignancies, i.e. leukaemia and lymphocytic lymphoma, were 1.5% for phlebotomy alone versus 10.9% for ^{32}P/phlebotomy and 17% for chlorambucil/phlebotomy. Thus, the risk of haematologic malignancies was markedly increased for patients treated with either of the two myelosuppressive regimens; especially so in the case of chlorambucil, which was associated with a statistically significant increase in the risk of developing acute leukaemia. Besides, there was also an increase in incidence of non-haematological malignancies in patients treated with chlorambucil and ^{32}P. Compared with patients in the phlebotomy group, the rate of cancer in chlorambucil- and ^{32}P-treated patients was 3 to 3.5 times and 2.3 to 2.5 times, respectively.[5] The types of cancer involved include those arising from the gastrointestinal (GI) tract, skin, breast, prostate, and kidney.[13]

PVSG-05 Study

The aim of this study was to test whether the addition of anti-platelet agents to phlebotomy could minimise the incidence of thrombotic complications. To this end, 166 eligible patients were recruited and randomised to treatment with phlebotomy plus aspirin 300 mg/day and dipyridamole 225 mg/day (Group A) or ^{32}P plus supplemental phlebotomy (Group B).

Seven patients had severe thrombotic complications in group A compared with 2 patients in group B. Similarly, six haemorrhagic complications occurred in group A, but none in group B. Thus, life-threatening thrombotic complications were not reduced, nor was it possible to show any decrease in thrombotic complications with the addition of anti-aggregating agents to phlebotomy. On the contrary, there was an increase in haemorrhagic complications with this regimen. The relative risk of thrombosis in group A was 3.6 times that in group B.

The overall cumulative failure rate (including severe thrombotic complications, haemorrhage, and death) with phlebotomy/anti-aggregation therapy was seven times higher than that with ^{32}P/phlebotomy; accordingly, the former protocol was prematurely terminated. It is now recommended that anti-aggregating agents should only be used for a short duration when there are signs of clinical aggregation, e.g. digital ischaemia.

In the light of the PVSG-01 and PVSG-05 study results, it was clear that myelosuppression remained an important component in the treatment of PV. However, in view of the increased incidence of neoplastic diseases in the ^{32}P- and chlorambucil-treated groups, a need for a safe myelosuppressive agent remained.

PVSG-08 Study

In 1977, the PVSG-08 study was initiated with the aim of studying the efficacy of hydroxyurea for the treatment of patients with PV. Hydroxyurea is a potent, non-alkylating myelosuppressive agent that inhibits deoxyribonucleic acid (DNA) synthesis via inhibition of ribonucleotide diphosphate reductase. It was hoped that hydroxyurea would be safe for long-term use because of its differing mechanism of action from alkylating agents.

In this study, 106 eligible patients were initially treated with a loading dose of hydroxyurea 30 mg/kg/day for 1 week, followed by 15 mg/kg/day. The dose was subsequently modified for cytopenia, or increased in increments of 5 mg/kg/day for adequate control of Hct. Periodic phlebotomies of 300-500 mL were permitted, although the aim was to do less than six per year. Half of the patients in this study received no prior myelosuppressive therapy, whereas the other half were previously treated with ^{32}P or some other myelosuppressive agent(s).

The results of this trial and the effectiveness of hydroxyurea as a myelosuppressive agent were reported by Donovan et al in 1984.[14] In terms of its efficacy in decreasing Hct, the study showed that 80% of patients with increased Hct achieved normal values within 12 weeks of starting hydroxyurea treatment. This study suggested, therefore, that hydroxyurea and supplemental phlebotomy could control blood counts for the majority of patients with PV.

In 1986, Kaplan et al reported the incidence of thrombosis among the 51 patients with PV in the PVSG-08

study who had been treated with hydroxyurea and phlebotomy, and compared them with the historical control group of 134 patients in the phlebotomy alone group of the PVSG-01 study.[15] The report showed that hydroxyurea and supplemental phlebotomy significantly diminished the risk of thrombosis compared with the historical controls treated with phlebotomy alone. During the first 378 weeks of the study, thrombotic events occurred significantly less frequently in patients treated with hydroxyurea (9.8%) than those managed with phlebotomy alone (32.8%).

Long-term Safety

In 1997, Fruchtman et al reported the incidence of leukaemic transformation for patients with PV treated with hydroxyurea.[11] During a median follow-up period of 9.6 years (maximum 15.3 years), patients only ever treated with hydroxyurea (i.e. no prior myelosuppressive treatment) and supplemental phlebotomy did not differ significantly from a historical control group treated with phlebotomy alone in terms of:

- the incidence of acute leukaemia
- the incidence of postpolycythemia myeloid metaplasia predicting for the development of acute leukaemia
- overall survival.

The conclusion is, therefore, that hydroxyurea is safe for long-term use.

Leukaemic Transformation in Polycythemia Vera

It has long been a controversial issue whether the occurrence of leukaemia in patients with PV reflects a fuller disease course due to prolonged survival, or is simply a complication of therapy. Landaw suggested that the treatment of PV with radiation or radiomimetic chemotherapy was associated with an increase in the incidence of acute leukaemia.[16] Lawrence et al on the other hand, considered that this increased incidence was explained by the longer survival in ^{32}P-treated patients, which permitted the more complete expression of the natural history of the disease.[17]

More recent studies indicate that this risk may in fact be treatment-related. The arguments in favour of this hypothesis are:

- the low incidence of leukaemia in subjects treated by phlebotomy[18]
- the similarity of chromosome damage(s) observed in the leukaemias occurring in ^{32}P-treated polycythemias compared with those observed in secondary leukaemias.[19]

TREATMENT RECOMMENDATIONS

There are several treatment recommendations based on the results of the PVSG studies:[4]

- because of the increased risk of thrombosis associated with age, patients older than 70 years are best treated with ^{32}P and supplemental phlebotomy
- patients younger than 50 years should be managed with phlebotomy alone, unless specific thrombosis-associated risk factor(s) are present. Myelosuppression with hydroxyurea seems advisable for younger patients provided they have a high phlebotomy requirement
- hydroxyurea should be considered for patients between 50 and 70 years old who have risk factor(s) present or a high phlebotomy requirement.

FUTURE TRENDS

The PVSG is no longer operating — its last meeting was in June 1994. Its files are now maintained at the Mount Sinai School of Medicine in New York City, NY, USA.[12] One member of the group, Najean, created the French (PV) study group, held a consensus conference in 1994,[20] and continued to explore new approaches to the treatment of PV. More recently, an Italian group has been formed [Gruppo Italiano Studio Policitemia Vera (GISP)], and has developed a study to evaluate lower doses of aspirin than used in the PVSG-05 protocol to determine whether the rate of vascular complications can be further reduced.

Anagrelide

Besides hydroxyurea, other (newer) agents have also been studied for the treatment of PV. Anagrelide, a quinazoline derivative, was initially developed as an inhibitor of platelet function. For patients with MPDs, 0.5-1.0 mg orally four times daily lowers the platelet count to less than 600 x 10^9 /L in 2 to 4 weeks in 90% of patients. At these doses, there is no measurable effect on platelet function. In contrast to ^{32}P, alkylating agents, and hydroxyurea, anagrelide does not typically lower the white cell count. Discontinuation of the drug results in a rapid return of thrombocytosis. Side effects of anagrelide include fluid retention, vasodilation with renal insufficiency, and frank congestive heart failure. At this juncture, its use in association with phlebotomy in PV is mainly to manage thrombocytosis in patients who are refractory to other myelosuppressive therapies.[21]

Recombinant Interferon Alpha

The rationale for using recombinant interferon alpha (IFN-α) is its myelosuppressive activity and its

putative ability to antagonise the action of platelet-derived growth factor (PDGF), a product of megakaryopoiesis that initiates fibroblast proliferation. This observation would suggest that IFN-α could, theoretically, modify the natural history of MPDs and reduce or delay the development of myelofibrosis.[22,23] However, because of its significant side effects, limitations associated with the subcutaneous mode of administration, and high cost, further studies are needed before IFN-α can be recommended for routine use in this disease.

CONCLUSIONS

Hydroxyurea is a safe and efficient agent for the treatment of the MPD PV. It carries little leukaemogenic risk and should be used for patients younger than 70 years who require frequent phlebotomies or have a thrombotic tendency. However, hydroxyurea is not without its drawbacks:

- the drug has to be taken regularly
- patients must scrupulously adhere to the schedule, as the line between an effective dose and one which produces unacceptable cytopenia can be very fine; this means that frequent monitoring of blood counts is mandatory
- some troublesome cutaneous side effects are also documented.

^{32}P is still a very effective form of treatment for elderly patients with PV. It induces a long period of remission with an excellent quality of life. Therefore, it remains the treatment of choice for patients older than 70 years. Apart from age considerations, ^{32}P is also indicated when hydroxyurea is badly tolerated or ineffectual, or when patients refuse/fail strict follow-up or to take their medication on a regular basis.

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