**Haematologica** 2000; 85:1011-1018
*original paper*

Hematology & Medicine

# Efficacy of pipobroman in the treatment of polycythemia vera: long-term results in 163 patients

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ABSTRACT

***Background and Objectives.*** **Polycythemia vera (PV) is a myeloproliferative disorder characterized by the expansion of the red cell mass. Our purpose was to evaluate the efficacy of pipobroman (PB) in the long-term control of PV and to assess early and late events.**

***Design and Methods.*** **From June 1975 to December 1997, 163 untreated patients with PV (median age 57 years, range 30-82) were treated with PB in a single Institute for a median follow-up of 120 months. The diagnosis was made according to the Polycythemia Vera Study Group criteria. PB was given at the dose of 1 mg/kg/day until hematologic response (hematocrit < 45% and platelets < $400\times10^9$/L) and of 0.3-0.6 mg/kg/day as maintenance therapy.**

***Results.*** **Hematologic remission was achieved in 94% of patients in a median time of 13 weeks (range 6-48). Median overall survival was 215 months, with a standardized mortality ratio of 1.7. The cumulative risk of death was 11%, 22%, and 26% at 7, 10, and 12 years, respectively. The incidence of thrombotic events was $18.4\times10^5$ person-years and the cumulative risk was 6%, 11%, 16%, and 20% at 3, 7, 10, and 12 years respectively. Acute leukemia occurred in 11 patients, myelofibrosis in 7, and solid tumors in 11. The 10-year cumulative risk of leukemia, myelofibrosis, and solid tumors was 5%, 4%, and 8%, respectively. In the logistic analysis age over 65 ($p = 0.0001$) and thrombotic events at diagnosis ($p = 0.001$) were significantly correlated with a higher risk of death. Female gender ($p = 0.02$) and age over 65 ($p = 0.01$) significantly influenced the occurrence of thrombotic complications. Age was the only significant risk factor for leukemia ($p = 0.04$) and for solid tumors ($p = 0.03$), while the duration of PB treatment did not influence these risks. No significant risk factor was demonstrated for myelofibrosis.**

***Interpretation and Conclusions.*** **This study demonstrates in a large series of patients, observed for a long period, that pipobroman is effective in the long-term control of PV. The risk of early thrombotic complications at 3 years is 6% and the 10-year risk of acute leukemia, late myelofibrosis, and solid tumors is 5%, 4%, and 8%, respectively. The duration of pipobroman treatment did not correlate with these events.**


Key words: polycythemia vera, pipobroman, thrombosis, acute leukemia, myelofibrosis.

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Polycythemia vera (PV) is a myeloproliferative disorder characterized by expansion of the red cell mass unrelated to any pulmonary, cardiac, renal or neoplastic disease. Several approaches have been used to confirm suspected PV. The initial criteria proposed by the *Polycythemia Vera Study Group* (PVSG) were applicable only to patients with overt disease[1] and have been reconsidered in the last 10 years after the introduction of more specific diagnostic techniques into clinical practice.[2] The course of PV has been well established by PVSG and GISP (*Gruppo Italiano Studio Policitemia*) studies.[3,4] A latent phase may precede the polycythemic phase, with a known risk of thrombosis and hemorrhage. The overt polycythemic phase can in turn develop into a spent phase. Metachronous neoplasms may lead to death in about 30% of patients with PV: acute leukemia is of particular prominence among such neoplasms.[4] Leukemia may be considered part of the natural history of the disease;[3] a relation, however, with the leukemogenic risk of prior therapy could be considered.[3-19] Historical data in untreated patients with PV indicate a life-expectancy of 18 months.[20] However, in the last decades, the survival of these patients has dramatically improved and has almost approached that of a matched population.[21] Different treatment strategies have been utilized for patients with PV, including phlebotomy and cytoreduction with either radiophosphorus or chemotherapy.[22-24] Nevertheless, there is no uniformly accepted approach to the management of the disease.[25] In the PVSG-01 randomized trial phle-

botomy was the only risk factor, in addition to advanced age and history of prior thrombosis, associated with a significant risk of early thrombotic accidents.[3] In addition, about 90% of phlebotomized patients tend to discontinue this treatment over time.[13] Cytoreduction, obtained with different agents such as chlorambucil,[3,6] radiophosphorus,[3,5,7,18,26] busulfan,[7,8] pipobroman,[9,10,15,19] and hydroxyurea,[11,14-18] is effective in reducing early thrombotic events but could increase the risk of cancer.[3,4] Anagrelide[27] and α-interferon[28] are promising agents still requiring long-term evaluation. The role of aspirin in the prevention of thrombotic complications is being evaluated by the *European Collaboration on Low-Dose Aspirin* (ECLAP) study.[29] Pipobroman (PB) is a piperazine derivative with a chemical formula related to alkylants. It acts as a metabolic competitor of pyrimidine bases and is of established effectiveness in the control of PV.[9,10,15,19] This paper illustrates the long-term results in 163 patients with PV homogeneously treated with PB, expanding and updating our original findings[10] with particular emphasis on late events.

## Design and Methods

This study was conducted at the Institute of Hematology of the University of Pavia between June 1975 and December 1997 and included 163 patients with PV treated with PB for more than 6 months. As of December 1998, the median follow-up was 120 months (range 12-248). Patients lost to follow-up (4%) were censored at the date of their last visit.

### *Diagnostic criteria*

The diagnosis of PV was made according to the PVSG criteria.[1] Culture studies (BFU-E and CFU-E) and the dosage of serum erythropoietin were introduced to diagnose PV in 1987 and 1990, respectively. Response to therapy was defined as a decrease of hematocrit to less than 45% and a decrease of platelets to less than $400\times10^9$/L. The diagnoses of acute leukemia (AL) and myelodysplasia were based on the French-American-British criteria.[30,31] Myelofibrosis (MF) was defined by the association of the following findings: leuko-erythroblastosis, anemia with tear-drop shaped red cells, splenomegaly, thrombocytopenia or thrombocytosis, extensive bone marrow fibrosis, systemic symptoms (fever, weight loss, bone pain). The diagnosis of solid cancer was based on a biopsy of the suspected lesion.

### *Treatment*

The induction dose of PB was 1 mg/kg/day orally until response. The maintenance dose varied between 0.3 and 0.6 mg/kg/day, according to response. Phlebotomy was utilized during the first months of treatment when hematocrit at diagnosis exceeded 55%. In 26 patients (16%) phlebotomy was added occasionally during the course of the disease prior to PB dose escalation. Although no fixed criteria for administration of antiaggregating agents were adopted, 56 patients (34%) received antiaggregating therapy at diagnosis with aspirin, dipyridamole, or ticlopidine.

### *Statistical methods*

Data are presented as mean and standard deviation for continuous variables, or median if skewed, and as absolute and relative frequencies for categorical variables. The following endpoints were considered for the analysis: a) time to thrombosis occurrence, b) time to leukemia development, c) time to myelofibrosis d) time to solid tumors e) time to death. Kaplan Meier estimation was used to calculate and plot the cumulative probabilities of survival and event-free survival; the cumulative hazard was also plotted. A Cox proportional hazard model was fitted to assess the univariate prognostic value of a series of candidate risk factors including: age, sex, hemoglobin, hematocrit, platelet count, white blood cell count, red cell mass, serum erythropoietin level, spleen and liver enlargement, plethora at diagnosis, thrombotic events prior to or at diagnosis, duration of PB therapy, phlebotomy. Hazard ratios (HR) with 95% confidence intervals (95% CI) were computed to measure the relative risk of the event in one category of the tested variable in respect of the reference category. For the same variables the incidence rate (expressed in number of events x person-months of observation) with 95% CI was also calculated. The standardized mortality ratio (SMR) with 95% CI was calculated in order to allow comparison of the observed mortality with the expected one, based on the probability of death in an age-and-sex-matched Italian population. The Stata 6.0 program (StataCorp College Station, TX, USA) was used for computations.

## Results

### *Patients*

The clinical characteristics of the 163 patients of this study are illustrated in Table 1. The male/female ratio was 1.5 and the median age of the patients was 57 years (range 30-82) with 17 of them under 40 years (10%). At diagnosis the mean value of hemoglobin and hematocrit was 19±2 g/dL and 57±6%, respectively. Leukocytosis (WBC $>12\times10^9$/L) and thrombocytosis (platelets $>400\times10^9$/L) were present in 53 patients (32%).

**Table 1. Characteristics of the patients.**

| | Number | % |
|---|---|---|
| Patients | 163 | |
| Male/female | 98/65 | 60/40 |
| Median follow up, months (range) | 120 (7-248) | |
| Median age, years (range) | 57 (30-82) | |
| Mean hemoglobin value (g/dL) | 19±2 | |
| Mean hematocrit value (%) | 57±6 | |
| Mean white blood cell value ($\times 10^9$/L) | 11±5 | |
| Mean platelet value ($\times 10^9$/L) | 357±256 | |
| Thrombocytosis (>400$\times 10^9$/L) | 53 | 32 |
| Leukocytosis (>12$\times 10^9$/L) | 53 | 32 |
| Enlarged spleen | 78 | 48 |
| Enlarged liver | 71 | 43 |
| Vascular accidents pre-PV | 29 | 18 |
| arterial | 22 | 14 |
| venous | 7 | 4 |
| Minor neurologic disturbances | 39 | 24 |
| Pruritus | 35 | 21 |
| Hypertension | 28 | 17 |
| Thrombosis at diagnosis of PV | 26 | 16 |
| arterial | 13 | 8 |
| venous | 13 | 8 |
| Hemorrhage | 5 | 3 |
| Myocardiopathy | 3 | 2 |
| No symptoms | 61 | 37 |

The mean value of WBC and platelet counts was 11±5$\times 10^9$/L and 357±256$\times 10^9$/L, respectively. Isolated splenomegaly was present in 31 patients (19%) and isolated hepatomegaly in 21 (12%). Fifty patients (31%) had liver and spleen enlargement. During the two years preceding the diagnosis of PV, vascular episodes occurred in 29 patients (18%) including 10 who suffered myocardial infarction, 6 angina pectoris, 6 an ischemic stroke or transient ischemic attacks, and 7 venous thrombosis. At diagnosis, the clinical features of the disease were as follows: minor neurologic disturbances such as dizziness, vertigo, paresthesia, headache, blurred vision, tinnitus in 39 patients (24%), pruritus in 35 (21%), hypertension in 28 (17%), venous thrombosis in 13 (8%), myocardial infarction or angina pectoris in 8 (5%), transient ischemic attacks or cerebral stroke in 5 (3%), hemorrhage in 5 (3%), and myocardiopathy in 3 (2%). Sixty-one patients (37%) were asymptomatic.

### *Efficacy*

Pipobroman induced a complete response in 153 patients (94%). The median time from the start of therapy to response was 13 weeks (range 6-48). After response, 142 patients (93%) received continuous maintenance therapy with PB to keep the hematocrit and hemoglobin within the normal ranges. In 11 patients, PB therapy could be withheld at the achievement of remission and was restored at disease expansion. Six responders (4%) developed resistance to PB after a median time of 80 months (range 36-165). They received busulfan 2-4 mg/day (3 patients, 3 responded), or hydroxyurea 500-1,000 mg/day (3 patients, 2 responded). In all the 53 patients presenting with thrombocytosis the response of the hematocrit was also accompanied in 2-4 months by normalization of platelet counts, which were maintained subsequently in the normal range by PB therapy.

### *Toxicity*

Pipobroman was well tolerated, with a good compliance. Blood counts were checked every 4-8 weeks. No acute toxicities after PB were documented. Grade 2 (WHO grading) leukopenia occurred in two patients and grade 4 thrombocytopenia in a single patient. Full hematologic recovery was obtained after PB discontinuation. The main PB toxicity was gastrointestinal, with 12 patients (7%) complaining of mild gastric pain or diarrhea. Two patients (1%) developed dermatologic side effects (dry skin and acne).

### *Late complications*

During the course of the disease, several adverse events occurred including cardiovascular complications in 10 patients (6%), minor neurologic symptoms in 17 (10%), thrombotic complications in 30 (18%), and secondary neoplasms in 29 (17%).

Cardiovascular events included hypertension in 6 patients and myocardiopathy with congestive heart failure in 4. All these events occurred in patients over 65, and 4 had histories of cardiovascular diseases. Minor neurologic symptoms, mainly attributable to hyperviscosity, consisted of paresthesia, headache, blurred vision and tinnitus. The incidence of thrombotic complications was 18.5$\times 10^5$ person-years, and the cumulative risk was 6%, 11%, 16%, and 20% at 3, 7, 10, and 12 years of observations, respectively (Figure 1a). The median age at occurrence of thrombosis was 61 years (range 30-77) and the male/female ratio 0.6. The median time from the onset of PV to thrombosis was 55 months (range 4-162). Forty-nine patients experienced thrombosis before the diagnosis of PV or at diagnosis and were at high risk of vascular accidents. Seven of these 49 patients (14%)

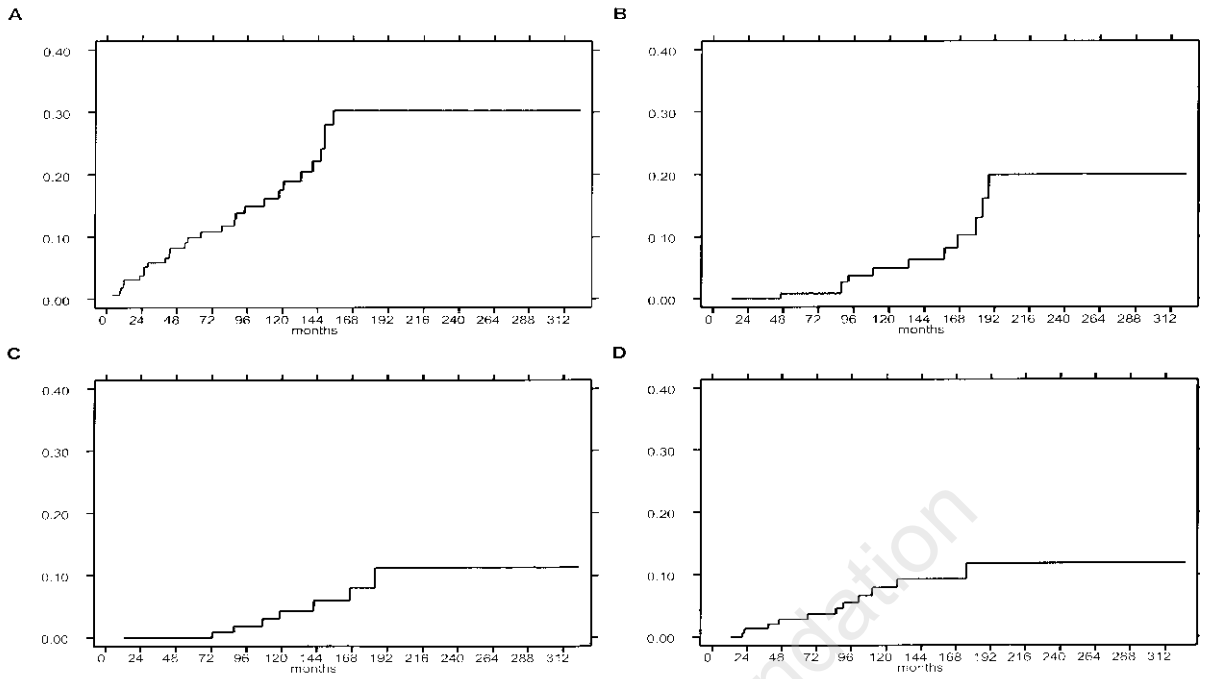


**Figure 1. Nelson-Aalen cumulative hazard model of thrombosis (A), leukemia (B), myelofibrosis (C) and solid tumors (D) in patients with polycythemia vera treated with pipobroman.**

developed thrombosis during PB treatment. Thrombotic episodes included: superficial thrombophlebitis of the lower limb in 13 patients, mesenteric thrombosis with intestinal infarction in 4, deep venous thrombosis of the lower limb in 3 (two of them had pulmonary embolism), ischemic stroke in 3, myocardial infarction in 3, transient ischemic attacks in 2, angina pectoris in 2. Seventeen of these complications were life-threatening. Secondary neoplasms consisted of acute leukemia (AL) in 11 patients (7%), solid tumors in 11 (7%), and myelofibrosis in 7 (4%). Table 2 illustrates the characteristics of the patients who developed subsequent neoplasms. The incidence of acute leukemia was $6.7\times10^5$ person-years and the cumulative risk was 1%, 5%, and 6% at 7, 10, and 12 years, respectively (Figure 1b). The median age at the occurrence of AL was 72 years (range 61-77) and the male/female ratio 0.6. The median time from the onset of PV to AL was 133 months (range 88-179). Acute leukemias were classified as myeloid in 10 patients (M1 in 4, M4 in 4, M5 in one, M6 in one), and as lymphoid in one. A myelodysplastic phase heralded AL in 2 patients, while in 2 patients AL developed after myelofibrosis. The patients who developed AL had been given PB for a median time of 100 months (range 88-165). Of the 3 patients who received PB-HU in sequence, none developed AL. The treatment with hydroxyurea lasted 7, 9, and 11 months. All 3 patients treated with busulphan after PB developed leukemia. Busulphan was administered in these 3 patients for 9, 16 and 44 months after 165, 100 and 100 months of pipobroman therapy, respectively. The median survival from the diagnosis of AL was 4 months (range 1-9). The incidence of myelofibrosis (MF) was $4.3\times10^5$ person-years, with a cumulative risk of 1%, 4%, and 6% at 7, 10, and 12 years, respectively (Figure 1c). The median age at the occurrence of MF was 66 years (range 54-68) and the male/female ratio 2.5. The median time from the onset of PV to MF was 119 months (range 88-166). Patients who developed MF had been given PB for a median of 98 months (range 42-172). The median survival from the diagnosis of MF was 18 months (range 5-31). The incidence of metachronous solid tumors (ST) was $6.8\times10^5$ person-years, with a cumulative risk of 4%, 8%, and 9% at 7, 10, and 12 years, respectively (Figure 1d). The median age at the occurrence of ST was 67 years (range 56-75) and the male/female ratio 2.6. The median time from the onset of PV to ST was 85 months (range 39-110). The patients who developed ST had been given PB for a median time of 70 months (range 19-100). Solid tumors were as follows: lung cancer in 5 patients, gastrointestinal tract cancer in 2, prostate, bladder, thyroid and skin cancer in one patient each.

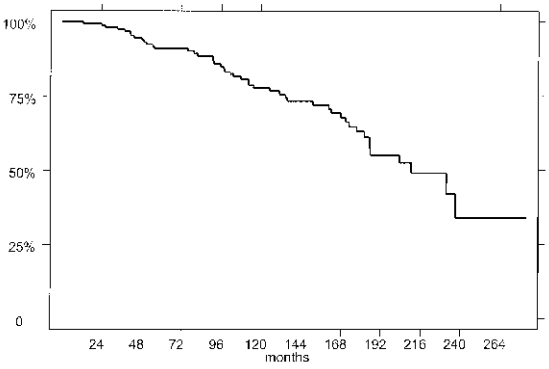


**Figure 2. Kaplan-Meier cumulative survival graph of patients with polycythemia vera treated with pipobroman.**

**Table 2. Clinical characteristics of patients who developed secondary neoplasms.**

| | *Acute leukemia* | *Myelofibrosis* | *Solid tumors* |
|---|---|---|---|
| No. of patients | 11 | 7 | 11 |
| Male/female ratio | 0.6 | 2.5 | 2.6 |
| Median age, years (range) | 72 (61-77) | 66 (54-68) | 67 (56-75) |
| Median time from PV diagnosis, months, (range) | 133 (88-179) | 119 (88-166) | 85 (39-110) |
| Median duration of PB therapy months, (range) | 100 (88-165) | 98 (42-172) | 70 (19-100) |
| Incidence ($\times 10^5$ person-years) | 6.7 | 4.3 | 6.8 |
| Cumulative risk at 7, 10, 12 years, % | 1, 5, 6 | 1, 4, 6 | 4, 8, 9 |
| Significant risk factors | Age | – | Age |

### *Survival and causes of death*

At the time of this analysis, 115 patients (71%) are alive. The median overall survival was 215 months; the actuarial overall survival was 89%, 78%, and 74% at 7, 10, and 12 years, respectively (Figure 2). The different causes of death are illustrated in Table 3 and include: AL in 11 patients (23%), thrombosis in 9 (19%), cardiovascular diseases in 6 (13%), ST in 5 (10%), MF in 4 (8%), and hemorrhage in 3 (6%). In 3 patients (6%) the cause of death was unrelated to PV, and in 7 (15%) it was unknown.

The age-and sex-standardized mortality ratio (SMR) was 1.7. This parameter showed a great variability between different age and sex groups, ranging from 4.6 for males aged 50-60 years to 0.3 for males over 70.

### *Analysis of risk factors*

In a logistic analysis, the relative risk of thrombosis was significantly influenced by female gender (HR=2.3; 95% CI: 1.08-7.91; $p$=0.02) and by age over 65 years (HR= 2.89; 95% CI: 1.30-6.42; $p$=0.01). The only variable influencing the risk of AL and ST was age (acute leukemia: HR=1.09; 95% CI: 1.02-1.16; $p$=0.04; solid tumors: HR=1.06; 95% CI: 1.01-1.12; $p$= 0.03). The duration of PB therapy did not significantly influence the risk of AL or ST. The shift from PB to busulphan seemed to influence the risk of AL, without reaching statistical significance (HR=3.0; 95% CI: 0.8-11.5; $p$=0.1). No significant risk factor was demonstrated for MF. The risk of death correlated with age over 65 (HR=1.06; 95% CI: 1.03-1.09; $p$=0.0001) and with the presence of thrombotic events at diagnosis (HR=2.9; 95% CI: 1.6-5.2; $p$=0.001).

**Table 3. Causes of death.**

| | *No. of patients* | *%* |
|---|---|---|
| Acute leukemia | 11 | 23 |
| Thrombosis | 9 | 19 |
| Cardiovascular complications | 6 | 13 |
| Solid tumors | 5 | 10 |
| Myelofibrosis | 4 | 8 |
| Hemorrhage | 3 | 6 |
| Unrelated | 3 | 6 |
| Unknown | 7 | 15 |
| Total | 48 | – |

## Discussion

In this study, pipobroman proved to be an effective treatment for patients with PV. This piperazine derivative induced a complete response in 94% of patients, with very mild toxicity and good compliance, allowing a median survival of 215 months. The 10-year cumulative risk of thrombosis was 16%, that of leukemia 5%, of myelofibrosis 4%, and of solid tumors 8%. These results, obtained in a cohort of patients treated for a median of 10 years, indicate that PB is effective in the long-term control of PV with a relatively low risk of thrombosis, myelofibrosis and subsequent neoplasms. The notion of the effectiveness of PB in PV goes back to the 1980s.[9–10] Accordingly, this drug has been used in large prospective studies.[15,19] Table 4 illustrates the results of PB in this study and in the two largest series of patients with PV treated with this agent. In one study of 199 PV patients followed for a median of 7.6 years,[19] all evaluable patients responded to PB. The median survival was 191 months from diagnosis and 37% of the patients developed disease-related complications including thrombosis, leukemia, myelofibrosis, and solid tumors. In particular, the 10-year cumulative risk of AL and of MF was 6% and 9%, respectively. The *French Polycythemia*

**Table 4. Results of pipobroman therapy in polycythemia vera.**

| *Results* | *This study* | *Najean, Rain[15] (FPSG)* | *Petti et al.[19]* |
|---|---|---|---|
| Complete response, % | 94 | 98 | 100 |
| Median survival, months | 215 | NR | 191 |
| 10-yr risk of thrombosis, % | 16 | 16 | NE |
| 10-yr risk of leukemia, % | 5 | 4 | 6 |
| 10-yr risk of myelofibrosis, % | 4 | 0 | 9 |
| 10-yr risk of solid tumors, % | 8 | 8 | NE |

*NR: not reached; NE: not evaluated.*

*Study Group* (FPSG) randomized 292 patients under 65 years old to receive PB or HU.[15] A good control of red cells and platelets was obtained in 90% and 78% of patients receiving PB and in 82% and 55% of those given HU. In the first 8 years of therapy, the cumulative risk of thrombosis was higher in the HU group than in the PB group, but the difference did not reach statistical significance. At 10 years, the risk of AL or ST was comparable in the two arms (4% and 8% for PB and 5% and 4% for HU, respectively), while the risk of MF was significantly higher in the HU arm (17%) than in the PB arm (0%). The 15-year cumulative survival was about 70% in both arms. The cumulative risk of thrombotic complications in our study was 6% at 3 years, 11% at 7 years, and 16% at 10 years, as in the FPSG study.[15] The problem of early thrombosis is of particular prominence in the management of PV patients. The PVSG-01 randomized study reported at 3 years a higher incidence of thrombotic events in the phlebotomy arm than in the $^{32}$P or the chlorambucil arms (thrombosis-free survival 75% versus 94%, respectively).[3] This study demonstrated that phlebotomy and phlebotomy rate were significant risk factors for thrombosis in addition to advanced age and history of prior thrombotic events.[3] The FPSG randomized trial on HU vs PB reported a slight excess of thrombotic complications from the 2$^{nd}$ to the 8$^{th}$ year of observation in the HU arm compared with the PB arm (from 3% to 12% for PB, and from 5% to 16% for HU).[15] Data concerning early thrombotic complications with interferon-$\alpha$[28] or anagrelide[27] cannot be considered conclusive and require larger studies. The impact of aspirin as an antiaggregating agent in the management of thrombotic complications in PV is under evaluation in prospective randomized studies.[29] The 10-year cumulative risk of leukemia after PB is between 4% and 6% (Table 4). Our results regarding the incidence of AL in PV are better than those reported after chlorambucil (13%)[3] or after radiophosphorus (10%),[3] and comparable to those observed after busulphan (3.5%).[7] The first findings of the PVSG-08 study with HU indicated an incidence of AL as low as 3.9%.[11] Subsequent studies,[14,17] however, and the updated PVSG-08 trial,[16] reported figures of risk of about 10% at 10 years of observation. The FPSG randomized trial on HU and PB reported that the risk of AL in PV using HU or PB therapy was essentially identical.[15] Patients with PV may develop AL as part of the natural history of their disease. According to the findings of the PVSG-01 study, the estimated risk of AL in patients treated with phlebotomy alone is 1.5%.[3] Myelosuppressive therapy may increase the risk of cancers to 6.7% as documented by the GISP study.[4] A significant correlation has been demonstrated in PV between the cumulative dose of $^{32}$P and the risk of leukemia,[5] while only a trend towards this correlation was observed for the cumulative dose of chlorambucil.[6] A recent FPSG study randomizing 461 patients to receive $^{32}$P alone or in association with HU, found a significantly higher risk of AL or ST in the combined therapy group, despite the reduction of the cumulative dose of radiophosphorus in the latter group.[18] This observation would support the concept that drug combination is more harmful in terms of risk of leukemia than the cumulative dose of a single agent *per se*.[12] In this study, the risk of subsequent leukemia was not influenced by the duration of PB therapy, while the use of two alkylators in sequence, such as PB-BU, seemed to influence the risk of AL, without reaching statistical significance.

A direct leukemogenic effect of myelosuppressive chemotherapy in PV is suggested by the presence in leukemia cells of cytogenetic abnormalities usually associated with mutagenic exposure such as chromosome 5 and/or 7 deletions[10,14] and by the deletion of the short arm of chromosome 17 (17p-).[32] This abnormality has recently been described in leukemias developing after essential thrombocythemia treated with HU[33] and in other neoplasms treated with non-alkylating agents.[32] Molecular studies in PV demonstrated an imbalance in the BCL-2 family.[34,35] These abnormalities may contribute to the pathogenesis of the disease, causing an accumulation of erythroid cells through the inhibition of apoptosis.[35] Leukemia in PV may eventually result from additional genetic abnormalities.

The risk of myelofibrosis in PV is significantly lower in patients treated with chemotherapy than in those treated with phlebotomy alone. At 15 years of observation patients receiving phlebotomy had a 75% risk of developing MF.[26] When phlebotomized patients subsequently received myelosuppression, the risk of progression to MF became similar to that observed in patients treat-

ed with $^{32}P$.[26] Besides, myelosuppression seems to avoid or to delay this evolution.[26] In this study with PB the 4% 10-year risk of MF is comparable with that found in other series of patients treated with this agent (0-8%)[15,19] and lower than that observed with HU (15%)[15] or radiophosphorus (12%).[18] Moreover, in the French study, hydroxyurea given after $^{32}P$ did not protect patients from progression to MF.[18] The authors supposed that the lack of control of the platelet count during the follow up (57% of patients developing MF had platelets > $400\times10^9$/L) had influenced the progression to MF.[18] In our experience pipobroman was effective in the long-term control of platelet counts. The advantage of pipobroman may derive from its activity on the megakaryocytic line[15] probably resulting in more efficient inhibition of the release of fibrogenic cytokines. In the present study the risk of solid tumor increased constantly over time, in accordance with the reports on other PV series.[3,4,7-19] The patient's age at diagnosis was the only variable significantly associated with the risk of subsequent solid tumors, while the duration of PB therapy did not influence this risk. Our study could not confirm Rozman's statement that the overall survival in PV is comparable with that of the normal population.[21] Indeed, the standardized mortality ratio in our study was 1.7, in accordance with that of the Italian Cooperative[4] and French studies.[15]

In conclusion, this report 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). The 10-year risk of acute leukemia, late myelofibrosis, and solid tumors is 5%, 4%, and 8%, respectively. The duration of PB treatment does not correlate with these events.

***Contributions and Acknowledgments***

*FP designed the study and wrote the paper. EB and ML helped to evaluate and interpret the data. FP, CIB and CK were responsible for the statistical analysis. FP, EB, ML, CIB, EO, AC, GC, SM, CB were involved in the recruitment of the patients. All the authors gave their critical contribution to the manuscript. ML and CaB revised the paper and gave final approval for its submission.*

***Disclosures***

*Conflict if interest: none.*

*Rebundant publication: no substantial overlapping with previous papers.*

***Manuscript processing***

*Manuscript received June 21, 2000; accepted September 2, 2000.*

***Potential implications for clinical practice***

- Pipobroman is a useful drug in front-line treatment of polycythemia vera and a definite alternative to hydroxyurea.[37]

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