

## Polycythemia vera in young patients: a study on the long-term risk of thrombosis, myelofibrosis and leukemia

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**Background and Objectives.** Polycythemia vera (PV) is unusual in young patients, so that little information is available on long-term clinical evolution in this particular group. The aim of this study was to define the long-term risk of thrombosis, acute leukemia (AL) and myelofibrosis with myeloid metaplasia (MMM) in young PV patients.

**Design and Methods.** From 1975 to 2000, 70 PV patients aged less than 50 years were followed for a median time of 14 years (range 2-26). About three quarters were treated with pipobroman. The Kaplan-Meier method and Cox regression were used for survival analysis. The standardized mortality ratio (SMR) was calculated using Italian age/sex specific mortality rates.

**Results.** The risk of thrombosis increased during the observation period, reaching a plateau of 14% at 10 years and was markedly higher in individuals with a previous history of thrombosis ( $p=0.0023$ ). No patient had progression into AL or MMM before the 9<sup>th</sup> year of follow-up. Subsequently, five patients (7%) developed AL and five (7%) MMM, with a 20-year cumulative risk of 15% and 10%, respectively. Overall survival at 20 years was 62%, with nine patients dying of progression into AL or MMM, four of vascular events, one of lung cancer, and four of non-PV-related causes. The SMR was 5.3, indicating a mortality significantly higher than that of the general population ( $p<0.000$ ).

**Interpretation and Conclusions.** This long-term retrospective cohort study shows that although the median survival of young patients with PV exceeds 23 years, their life expectancy is markedly lower than that of the general population because of disease evolution into AL or MMM.

**Key words:** chronic myeloproliferative disorders, polycythemia vera, young patients, thrombosis, second malignancies.

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Polycythemia vera (PV), a myeloproliferative disorder with a poorly understood pathogenesis,<sup>1</sup> predominantly affects people in the 6<sup>th</sup> decade of life, but nearly a fifth of the patients are diagnosed with PV before the age of 50.<sup>2</sup> This category of patients with a relatively long life expectancy is exposed to the complications of the disease itself and to the long-term sequelae of treatment. The two most relevant problems of patients with PV are the risk of life-threatening thrombosis<sup>3</sup> and that of the disease progressing into acute leukemia (AL) or myelofibrosis with myeloid metaplasia (MMM).<sup>4-5</sup> Young age *per se* seems a protective factor for thrombosis.<sup>2</sup> The thrombotic risk, directly related to the hematocrit value,<sup>6</sup> however, is increased in PV patients over 40 years of age<sup>2</sup> and in those treated with phlebotomy.<sup>3,7</sup> Phlebotomy remains the most applied treatment in younger patients.<sup>5,8</sup> Transition to AL or MMM could be part of the natural evolution of PV.<sup>7</sup> Leukemic transformation, however, may be related to exposure to myelo-suppressive agents, a relationship particularly evident with <sup>32</sup>P or chlorambucil,<sup>7</sup> but less evident with hydroxyurea,<sup>9</sup> pipobroman<sup>10</sup> or busulphan.<sup>11</sup> MMM appears to occur more frequently in patients treated with phlebotomy<sup>7</sup> or hydroxyurea<sup>9</sup> than in those treated with pipobroman.<sup>10</sup>

Only few studies are available on the long-term evolution of PV in younger patients,<sup>12-14</sup> most of them with a relatively low patient accrual. This study reports the long-term outcome in terms of survival, thrombosis, and evolution to AL or MMM, of a series of 70 PV patients younger than 50 years consecutively diagnosed and followed in a single Center for a median time of 14 years.

### Design and Methods

This study includes 70 patients with PV, aged less than 50 years, consecutively diagnosed at the Division of Hematology, Policlinico San Matteo, University of Pavia, between 1975 and 2000. All patients were registered on a clinical chart and followed from the time of diagnosis to the data of last follow-up visit. These patients aged < 50 years accounted for one third of the patients with PV consecutively diagnosed and followed in the same period at our Center. As of April 2002, the median follow-up was 14 years (range 2-26) with no patient lost.

### Diagnostic criteria

The diagnosis of PV was made according to the PVSG criteria.<sup>15</sup> Culture studies (BFU-E and CFU-E) and dosage

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of serum erythropoietin were introduced into the diagnostic procedure in 1987 and 1990, respectively. Response to therapy was defined by a decrease of hematocrit to less than 45% and of platelets to less than  $400 \times 10^9/L$ . The diagnosis of AL was based on the French-American-British criteria.<sup>16</sup> MMM 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, and systemic symptoms (fever, weight loss, bone pain). The diagnosis of solid tumor (ST) was based on biopsy results of the suspected lesion.

### Treatment

The majority of patients (82%) received a front-line treatment with myelosuppressive agents. The median follow-up time for these patients was 15 years (range 2-26). In detail, 51 patients (73%) received pipobroman (PB), an effective drug in both PV<sup>10</sup> and essential thrombocythemia,<sup>17</sup> and 6 (9%) hydroxyurea (HU) with induction doses of 0.7-0.9 mg/kg/die and 15 mg/kg/die, respectively. Patients received a variable maintenance dose of the above drugs to control the disease. Phlebotomy was the sole treatment in 13 more recently diagnosed patients (18%) who had no vascular risk factors at diagnosis, no vascular complications during follow-up, and had stable disease. The median follow-up time for these patients was 3 years (range 2-18). Occasionally, phlebotomy was added to myelosuppressive drugs in 22 patients (31%). Although no fixed criteria for the use of antiaggregating agents were adopted, 41 patients (58%) received low-dose aspirin from diagnosis.

### Statistical analysis

Continuous variables are summarized as medians and ranges, when skewed, or as means and standard deviations (SD). Categorical variables are reported as counts and relative frequencies. Survival analysis was performed in the whole population of young PV patients, without separating them according to the treatment received (phlebotomy or myelosuppressive agents). In fact, the wide variation in the number and median follow-up of patients in the two groups did not allow statistically significant conclusions to be drawn on differences in term of thrombosis or second malignancies. Survival analysis was carried out considering the following end-points from the start of follow-up: first thrombosis, diagnosis of AL, of MMM, of ST, and death from all causes. Actuarial risk was computed as a cumulative hazard. The Kaplan-Meier product-limit method was used to estimate the cumulative probability of event-free survival. The incidence rate with the corresponding 95% confidence interval (CI) was also computed for each end-point. The mortal-

ity observed in the cohort of patients under study was compared to that expected according to the Italian age- and sex-specific mortality rates by means of the standardized mortality ratio (SMR) and its corresponding 95% CI. Finally, Cox proportional hazard regression was used to investigate the association between each end-point and the following risk factors: sex, age at diagnosis, vascular events before or at diagnosis, liver and/or spleen enlargement, hemoglobin value, hematocrit value, red blood cell count, platelet count, white blood cell count, phlebotomy, and duration of treatment with myelosuppressive agents. Because of the relatively small number of patients, no multivariate analysis was performed. Hazard ratios (HR) with 95% CI were computed to assess the relative risk of the end-point event in each level of the tested risk factor, with respect to a reference level. All computations were carried out using STATISTICA for Windows 5.5 software from StatSoft Inc., 2000.

## Results

### Patients

The clinical features of the 70 young patients of this study are illustrated in Table 1. Vascular complications, when existing, had occurred between 1 and 95 months (median 18 months) before the diagnosis of PV. These complications included: myocardial infarction in five patients, *angina pectoris* in one, ischemic stroke or transient ischemic attacks in two, thrombosis of peripheral arteries in one, and venous thrombosis in three. Vascular episodes at PV diagnosis were as follows: minor neurological symptoms such as headache, vertigo, paresthesia, tinnitus, blurred vision in 11 patients (15%), myocardial infarction in two (3%), *angina pectoris* in one, thrombosis of the hepatic veins in one, and venous thrombosis of the lower limbs in one. Of particular clinical interest was the favorable outcome of a 30-year old woman with thrombosis of the hepatic vein who was successfully managed with HU, heparin, and portal-systemic shunting. Hemorrhage occurred in three patients (4%). At diagnosis 11 patients (15%) had pruritus, five (7%) hypertension, and three (4%) cardiomyopathy.

### Treatment outcome

All patients had blood counts checked every 4-8 weeks. PV was well controlled by the different treatments offered, without any significant toxicity. Response was achieved in 56 of 57 patients (98%) who received chemotherapy. One patient did not respond to HU and subsequently received PB. PB and HU were well tolerated. Patients treated with phlebotomy alone underwent a median of 3-4 procedures per year with the aim of maintaining hematocrit values below 45%.

### Thrombosis and malignancies during follow-up

During the course of PV, thrombotic events occurred in eight patients (11%), five of whom (62%) had had a prior thrombosis. All patients who had thrombosis were receiving myelosuppressive agents. These events included: two ischemic strokes (one fatal), two myocardial infarctions (one fatal), one splenic infarction, one mesenteric thrombosis with intestinal infarction, and two venous thromboses (one superficial thrombophlebitis and one deep vein thrombosis complicated by pulmonary embolism). As shown in Table 2, the median age at the occurrence of thrombosis was 47 years (range 30-55) with a male/female ratio of 7/1. The median time elapsed from diagnosis of PV to thrombosis was 2.2 years (range 0.8-9.3). During follow-up the incidence of thrombosis was 9.2/1000 patient-years (95% CI: 4.6-18.3), and the actuarial risk, shown in Figure 1, was 14% between the 10th and 20th year of observation. A history of thrombosis (thrombosis before or at diagnosis of PV) was the only risk factor significantly associated with thrombosis during follow-up (HR = 9.3; 95% CI: 2.2-39.2;  $p = 0.0023$ ). Malignancies occurred in 11 patients (15%). These consisted of AL in five patients (7%), MMM in five (7%), and lung cancer in one (1%). All leukemias were of myeloid type. The median age at diagnosis of AL was 61 years (range 52-62) and the male/female ratio 3/2. The median time from diagnosis of PV to AL was 16 years (range 11-22). In one patient PV progressed into AL through a short myelodysplastic phase, and in another through a 2-year phase of MMM. Patients who developed AL had received myelosuppressive therapy for a median period of 14 years (range 9-20). The incidence of AL was 5.4/1000 patient-years (95% CI: 2.2-13), and the actuarial risk was 0% and 15% at, respectively, 10 and 20 years of observation (Figure 1). The median survival from diagnosis of AL was 4 months (range 1-13). No statistically significant risk factors (including duration of exposure to myelosuppressive agents) were identified for the occurrence of leukemia. MMM occurred in five patients at the median age of 54 years (range 50-64), with a male/female ratio of 4/1. The median time from diagnosis of PV to MMM was 12 years (range 9.8-21.6). These patients had received myelosuppressive agents for a median of 18 years (range 11.5-22). The incidence of MMM was 5.4/1000 patient-years (95% CI: 2.2-13) and the actuarial risk was 4% and 10% at 10 and 20 years of observation, respectively (Figure 1). One patient developed AL two years after the diagnosis of MMM. The median survival from the diagnosis of MMM was 16 months (range 2-43). Leukocytosis at diagnosis was significantly associated with the occurrence of MMM (HR = 1.5; 95% CI: 1.1-2;  $p = 0.003$ ). A 52-year old female patient with a smoking history developed a lung cancer after 9.2 years of PV and 8.1 years of myelosuppressive therapy.

**Table 1. Baseline characteristics of 70 young patients with polycythemia vera.**

	N.	%
Patients	70	—
Male/female	49/21	—
Median follow-up, years (range)	14 (2-26)	—
Median age, years (range)	42 (18-49)	—
Mean hemoglobin (g/dL)±SD	21±2	—
Mean hematocrit (%)±SD	60±5	—
Mean white cell count ( $\times 10^9/L$ )±SD	12±3	—
Mean platelet count ( $\times 10^9/L$ )±SD	544±186	—
Splenomegaly	29	41
Hepatomegaly	28	40
Vascular accidents before diagnosis		
Arterial thrombosis	9	13
Venous thrombosis	3	4
Vascular accidents at diagnosis		
Arterial thrombosis	3	4
Venous thrombosis	2	3
Hemorrhage	3	4
Minor neurological disturbances	11	15
No clinical symptoms	33	47

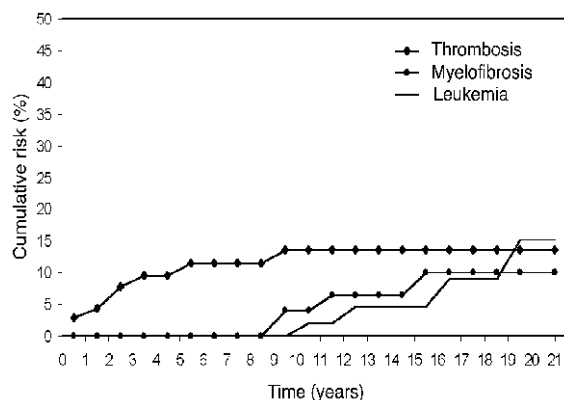
**Table 2. Follow-up findings of 70 young patients with polycythemia vera.**

	Thrombosis	Leukemia	Myelofibrosis
N. of patients, sex (M/F)	8 (7/1)	5 (3/2)	5 (4/1)
Median age, years (range)	47 (30-55)	61 (52-62)	54 (50-64)
Duration of PV, years (range)	2.2 (0.8-9.3)	16 (11-22)	12 (9.8-21.6)
Incidence, /1000 p-y	9.2	5.4	5.4
10- and 20-year cumulative risk	14%, 14%	0%, 15%	4%, 10%
Risk factor at diagnosis	Thrombosis	None	Leukocytosis

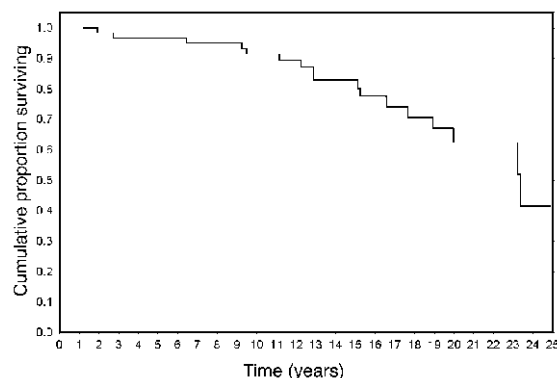
ing history developed a lung cancer after 9.2 years of PV and 8.1 years of myelosuppressive therapy.

### Survival and causes of death

At the time of this analysis 52 patients (74%) were still alive. The overall survival at 10, 15, and 20 years was 91%, 83%, and 62%, respectively (Figure 2). The cause of death was evolution of disease to AL or MMM in 9 patients (50%), thrombosis in two (11%), hemorrhage in two (11%), lung cancer in one (5%), and non-PV-related in four (22%). The age- and sex-standardized mortality ratio was 5.3 (95% CI: 3.3-8.5), which was significantly higher than that of the general Italian population ( $p < 0.000$ ).



**Figure 1.** Cumulative risk of thrombosis, myelofibrosis with myeloid metaplasia and leukemia in 70 young patients with polycythemia vera.



**Figure 2.** Survival estimate of 70 young patients with polycythemia vera.

## Discussion

Clinical information on long-term events in young individuals with PV is limited.<sup>12-14</sup> Because of their relatively long life expectancy, younger patients are more exposed to the complications of the disease itself and to the long-term sequelae of therapy. The risk of life-threatening thrombosis and that of progression to acute leukemia or myelofibrosis with myeloid metaplasia are the two most relevant problems.<sup>4-5,8</sup>

We report the outcome of a cohort of 70 consecutive PV patients less than 50 years of age followed for a median of 14 years. We observed a 7% rate of thrombosis at diagnosis, which is similar to that reported by Najean *et al.*<sup>12</sup> This rate, however, was 24% if we include the thrombotic episodes that occurred before diagnosis. In our series of patients, almost all treated with myelosuppressive drugs, the incidence of thrombosis during follow-up was 9.2/1000 patient-years. This incidence was quite different from that reported by Perea *et al.*<sup>14</sup> in patients mostly treated with phlebotomy, estimated at about 40/1000 patient-years. The risk of thrombosis showed a peculiar profile, increasing during follow-up and plateauing at 14% after 10 years. This behavior seems a characteristic of younger PV patients, while in series that include patients of all ages the thrombotic risk shows a constant increase over time.<sup>7,10</sup> In this series, a history of thrombosis was a statistically significant risk factor for the occurrence of thrombotic complications during the course of the disease. Therefore, patients with a history of thrombosis represent a subset who may benefit from myelosuppressive drugs rather than phlebotomy to control the disease, although cytotoxic drugs seem unable to prevent thromboembolic events completely. A

history of thrombosis has been shown to be a risk factor for subsequent vascular events in series including PV patients of all ages.<sup>2,7,18</sup> Our study confirms the prognostic relevance of this factor also in young patients. We cannot draw any conclusion on the role of antiaggregating agents in lowering the risk of thrombosis in younger PV patients. The ongoing European double-blind study with aspirin will clarify this issue.<sup>19</sup>

The risk of developing AL and MMM is the most relevant issue in the long-term follow-up of younger patients with PV. In this study, no case of transformation was observed before the 9<sup>th</sup> year from diagnosis, so that an initial safe period could be envisaged. However, the risk of developing AL and MMM at 20 years was 15% and 10%, respectively, with a continuous increase over time. The occurrence of AL in young patients has been evaluated in other studies,<sup>12,13</sup> but a realistic evaluation of this problem is often hampered by the relatively short follow-up. MMM has been reported to occur earlier and more frequently in young PV patients when phlebotomy is the main treatment.<sup>12</sup> It is known that AL and MMM may represent a natural evolution of PV.<sup>7</sup> These complications could be more evident in young patients with PV due to the longer duration of the disease *per se*. Nevertheless, the use of chemotherapeutic agents, although effective in the control of myeloproliferation and the risk of thrombosis,<sup>7</sup> may play a role in the occurrence of AL. Results of cytogenetic studies in patients with post-PV AL who received cytotoxic drugs are in favor of the leukemogenic effect of these agents.<sup>20,21</sup> This is particularly evident with <sup>32</sup>P and busulphan.<sup>7,22</sup> Although it is difficult to assume that one agent is better than another,<sup>5</sup> HU<sup>23</sup> and PB<sup>10</sup> seem to be less leukemogenic agents. Concerning the risk of MMM, a French randomized

study<sup>9</sup> demonstrated that patients receiving PB have a significantly lower risk than those receiving HU. In this study we did not find a statistical correlation between duration of exposure to chemotherapeutic agents and the occurrence of AL or MMM.

The median survival from diagnosis of PV patients ranges between 15 and 18 years in series including patients of all ages.<sup>2,9,10</sup> In this study, the median survival of PV patients aged less than 50 was 23 years, with 62% of the patients still being alive 20 years after diagnosis. However, the standardized mortality ratio of 5.3 indicates a substantial reduction of life expectancy with respect to the general population of corresponding age. Concerning the cause of death, while the general population of PV patients shows an excess of death from vascular complications with a vascular event/malignancy ratio of 1/0.8,<sup>2</sup> PV patients under 50 years show an excess of death from malignancy with a vascular event/malignancy ratio of 1/2.5. The long-term exposure to myelosuppressive agents could play a causative role in this excess of mortality from malignancy. In young patients, an increasing risk of death because of malignancies has been reported by Finazzi *et al.*<sup>24</sup> Survival of young patients whose disease progresses to AL or MMM is similar to that of older patients undergoing the same complication.<sup>10,25</sup> In our series it was 4 and 16 months for AL and MMM, respectively. The introduction of hematopoietic stem cell transplantation for younger patients who develop AL or MMM could offer an option for prolonging survival.<sup>26-27</sup>

In conclusion, this long-term study on young individuals with PV, most treated with myelosuppressive agents, shows a median survival of 23 years. The standardized mortality ratio, however, indicates a statistically significant reduction of life expectancy when compared with that of the general population of the same age. The risk of thrombosis reaches 14% at 10 years, plateauing thereafter. The 20-year risk of AL and MMM in these young patients is 15% and 10%, respectively. These hematologic transformations, although delayed, have a major impact on survival.

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## Pre-publication Report & Outcomes of Peer Review

### *Contributions*

FP and ML were the main investigators who designed the study. FP and LM collected and interpreted the data. CP was responsible for the statistical analysis. FP wrote the paper. FP, LM, EO, CB, AC, EB, MB, LA, SC and ML were responsible for the clinical care of the patients. All the authors gave their critical contribution to the manuscript. ML revised the paper and gave final approval for its submission.

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### *Disclosures*

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous paper.

### *Manuscript processing*

This manuscript was peer-reviewed by two external referees and by Professor Jerry L. Spivak, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Spivak and the Editors. Manuscript received August 16, 2002; accepted November 13, 2002. In the following paragraphs, professor Spivak summarizes the peer-review process and its outcomes.

### *What is already known on this topic*

The natural history of polycythemia vera is less well documented than it needs to be and there are several studies that suggest that the disease may have a different clinical course in younger individuals. However, most of these studies involved small groups of patients with a limited observation period and all have been retrospective.

### *What this study adds*

Passamonti's study is the largest to date of polycythemia vera patients under the age of fifty and the one with the longest follow-up. The study reinforces the notion that cytotoxic chemotherapy should be avoided to as great an extent as possible because of the risk of acute leukemia and bone marrow failure.

### *Caveats*

As with previous studies, Passamonti's study was retrospective and since most patients received chemotherapy, it was not possible to determine the exact extent to which treatment, as opposed to disease, contributed to the complication rate.