Cardiovascular Risk in Polycythemia Vera: Thrombotic Risk and Survival: Can Cytoreductive Therapy Be Useful in Patients with Low-Risk Polycythemia Vera with Cardiovascular Risk Factors?

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Keywords

Cardiovascular risk · Polycythemia vera · Cytoreduction

Abstract

Background/Aims: Cardiovascular risk factors are not considered in the current scores for evaluation of the thrombotic risk in myeloproliferative neoplasms, and in polycythemia vera (PV) in particular. Cytoreduction is currently not indicated in low-risk patients with PV, despite the absence or presence of cardiovascular risk factors. Our purpose is to highlight how cardiovascular risk factors in patients with PV increase the thrombotic risk both in low- and high-risk patients. **Methods:** We collected and analyzed data from 165 consecutive patients with a diagnosis of PV followed at our institution and compared the frequency of thrombosis in subgroups of patients distinguished by the presence or absence of cardiovascular risk factors. The statistic tools used to obtain the results were the χ^2 and the Kruskal-Wallis test for frequencies, and the Kaplan-Meier method as well as the log-rank test for analysis of survival data. **Results:** The major result obtained is that the frequency of thrombotic events in our population is strictly linked with the cardiovascular risk, and it increases with the number of risk factors. Moreover,

survival significantly worsens with the number of cardiovascular risk factors, despite the classical PV risk stratification.

Conclusion: It should be useful to design perspective studies to determine the real influence of cardiovascular risk factors on the thrombotic risk for patients with PV and on survival in order to evaluate the opportunity to develop new specific therapeutic recommendations.

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Introduction

The diagnosis of polycythemia vera (PV) often requires the presence of JAK2 mutation, in addition to the increase of hemoglobin/hematocrit ratio, whose threshold levels have been established by the 2016 World Health Organization (WHO) revised criteria (>16.5 g/dL or $>49\%$ for males and >16 g/dL or $>48\%$ for females) [1, 2]. Almost all patients with PV harbor a JAK2 mutation; approximately 96 and 3% of them display somatic activating mutations in exon 14 (JAK2-V617F) and JAK2 exon 12, respectively. In a recently published study conducted on 826 Mayo Clinic patients with essential thrombocythemia (ET), PV, or primary myelofibrosis, the respective

Table 1. Characteristics of the 165 PV patients included in the study

	N (%)
Females	60 (36.7)
Males	105 (63.6)
Age in years, range	62.8 (18.4–97.2)
JAK2 V617F	153 (92.7)
JAK2 E12	5 (3)
JAK2 wild-type	7 (4.2)

Table 2. CVR in the 165 PV patients included in the study

CVR factor	N (%)
Smoke	25 (15)
Hypertension	105 (63.7)
Obesity	12 (7.5)
Dyslipidemia	47 (28.7)
Diabetes	28 (16.9)

median survivals were approximately 20 years for ET, 14 years for PV, and 6 years for primary myelofibrosis [3]. The increased risk of vascular complications over time is the main clinical feature of PV. With regard to PV, two risk categories are defined. In particular, the low-risk category applies for patients without a history of thrombosis and younger than 60 years, and the high-risk category for patients older than 60 years and/or with a history of thrombosis. All patients with PV should be managed with phlebotomy to maintain the hematocrit at <45% and take low-dose aspirin. Cyto-reduction is indicated in high-risk patients. Current classifications of the thrombotic risk in patients with PV do not consider cardiovascular risk (CVR), and therefore the presence of CVR factors does not currently influence the choice of a cytoreductive therapy. In this study, we evaluated the frequency of CVR in a group of patients with PV and the possible impact of the CVR on survival.

Patients and Methods

From January 1997 to May 2019, 165 consecutive patients with PV were followed at our institution with a median follow-up of 58.18 months (0.3–289.3 months). We evaluated, with retrospective analysis, the main characteristics of the study population such as gender, age, and mutational status along with CVR frequency, considering cigarette smoking habits, hypertension, diabetes, obesity, and dyslipidemia. In particular, patients with only one of these conditions were distinguished by those with none or >1 cardiovascular risk factor. Moreover, the correlation of these cardiovascular risk conditions with the onset of thrombosis has been evaluated. The frequencies were calculated by using the χ^2 method and the

medians comparison through the Kruskal-Wallis test. Furthermore, the Kaplan-Meier method was used to evaluate survival, and the comparison between survival curves was studied with the log-rank test.

Results

The main features including sex, median age, and the mutational status, along with the cardiovascular risk factors of the cohort under examination were, respectively, summarized in Tables 1 and 2. In particular, 37 PV patients (22.42) have no CVR, while 66 PV patients (49%) have only one cardiovascular risk factor, and 62 (37.57%) have >1 CVR. In patients with PV, we highlighted 49 (29.69%) cases of thrombosis at diagnosis or before diagnosis and 16 (9.69%) cases of thrombosis after diagnosis. Overall, PV patients show a thrombosis frequency of 65/165 (39.39%).

In the examined patients, cytoreduction was prescribed in patients with high-risk PV, according to ELN recommendations. Of the 119 patients with high-risk PV, 95 received hydroxyurea (HU) as first-line cytoreductive therapy, while 22 were prescribed with ruxolitinib after first-line HU because of HU intolerance (18 patients) or HU resistance (4 patients). All of the 165 patients received antiplatelet agents (117 patients) or anticoagulant drugs (65 patients). Between the antiplatelet agents prescribed, aminosalicylic acid was the most used (in 84 patients). The remaining 33 patients treated with antiplatelet agents received ticlopidine (27 cases) or clopidogrel (6 cases). Between the 65 patients treated with anticoagulant therapies, 44 received anti-vitamin K agents (warfarin or dicoumarol) and 21 patients received direct oral anticoagulants.

In our patients with PV, the frequency of thrombotic episodes is strictly correlated with cardiovascular risk factors. In fact, in PV patients without CVR, thrombosis is present in 8 of 37 cases, and 21 of 66 cases in patients with only one CVR, and 26 of 62 cases in patients with >1 CVR. Our data also show a significant correlation between cardiovascular risk factors and survival in the cohort of patients with PV, distinguished by number of cardiovascular risk factors (Fig. 1).

Discussion and Conclusions

Patients with myeloproliferative neoplasms (MPNs) have an increased risk of thrombotic events if compared with the general population, with a greater risk of MPNs-associated morbidity and mortality [4, 5]. A recent single-center study conducted on 526 patients with MPNs with an overall study period of 3,497.4 years, reported an inci-

Fig. 1. Survival and CVR in PV patients.

dence rate of 1.7% of venous thrombosis per patient/year [6]. Overall, 38.4% of all venous thromboses occurred before or at diagnosis of MPNs, with 55.6% occurring at uncommon sites such as splanchnic or cerebral veins. PV is a MPN respectively characterized by erythrocytosis and thrombocytosis; other clinical features include leukocytosis, splenomegaly, thrombosis, bleeding, microcirculatory symptoms, pruritus, and risk of leukemic or fibrotic transformation. Moreover, thrombosis and cardiovascular disease are more prevalent in PV than in other myeloproliferative disorders. It has been estimated that 30–50% of PV patients have minor or major thrombotic complications, and vascular mortality accounts for 35–45% of all PV-related deaths [7]. Determining the thrombotic risk in PV has a pivotal importance to achieve a proper therapeutic choice. In PV, two risk categories are considered: high-risk (age >60 years or history of previous thrombosis) and low-risk (absence of both risk factors). In a previously proposed thrombotic risk classification model, an intermediate-risk category was added to the traditional high-risk and low-risk category, fitting patients aged <60 years, with no history of thrombosis, in presence of cardiovascular risk factors [8]. This thrombotic risk classification model did not achieve higher consideration, and it is not currently used in clinical practice. Cerquozzi et al. [9] explored the association of cardiovascular risk factors with the occurrence of arterial or venous events at or following diagnosis: they found that older age (≥ 60 years), hypertension, diabetes, hyperlipidemia, and normal karyotype were associated with arterial events, whereas younger age (<60 years), female sex, palpable splenomegaly, and history of major hemorrhage were associated

with venous events. Today, for patients with PV aged <60 years and with one or more cardiovascular risk factors, there is no indication for cytoreductive therapy. In ET, the IPSET-thrombosis system that includes age, previous thrombosis, cardiovascular risk factors, and JAK2-V617F mutation, is the recommended prognostic system and it should be scored in all patients at diagnosis. This implies that general risk factors for thrombosis, including smoking habits, diabetes mellitus, arterial hypertension, and hypercholesterolemia, should also be considered, even in the absence of specific therapeutic indications [10]. Recently, a panel of experts is questioning the traditional classification of thrombotic risk in PV; a matter of discussion is whether these definitions predicting thrombotic risk are still valid and whether the newly proposed disease-related risk factors, such as cardiovascular risk factors, leukocytosis, JAK2V617F allele burden, may improve the grading system of the thrombotic risk [11].

According to our experience, it should be useful to design perspective studies to determine the real influence of CVR on the thrombotic risk in patients with PV and on survival in order to evaluate the opportunity to develop new specific therapeutic recommendations, such as early cytoreduction, for patients with PV aged <60 years and having cardiovascular risk factors.

Statement of Ethics

This study was approved by our hospital's Ethics Committee ("Palermo 1"). Patients have given informed consent to participate to this research.

Disclosure Statement

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Author Contributions

S.M.: study design, writing of the paper, and revision. M.S.: collecting data and paper revision. V.A.: data elaboration and writing of the paper. G.A. and S.R.: data collection. F.P., A.P., and M.B.: data generation and collection. A.R. and S.S.: paper revision.

References

- 1 Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016 May;127(20):2391–405.
- 2 Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2019 Jan;94(1):133–43.
- 3 Tefferi A, Guglielmelli P, Larson DR, Finke C, Wassie EA, Pieri L, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood*. 2014 Oct;124(16):2507–13.
- 4 Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. *Blood*. 2013 Sep;122(13):2176–84.
- 5 Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol*. 2005 Apr;23(10):2224–32.
- 6 Wille K, Sadjadian P, Becker T, Kolatzki V, Horstmann A, Fuchs C, et al. High risk of recurrent venous thromboembolism in BCR-ABL-negative myeloproliferative neoplasms after termination of anticoagulation. *Ann Hematol*. 2019 Jan;98(1):93–100.
- 7 Vannucchi AM. Insights into the pathogenesis and management of thrombosis in polycythemia vera and essential thrombocythemia. *Intern Emerg Med*. 2010 Jun;5(3):177–84.
- 8 Finazzi G, Barbui T. Risk-adapted therapy in essential thrombocythemia and polycythemia vera. *Blood Rev*. 2005 Sep;19(5):243–52.
- 9 Cerquozzi S, Barraco D, Lasho T, Finke C, Hanson CA, Ketterling RP, et al. Risk factors for arterial versus venous thrombosis in polycythemia vera: a single center experience in 587 patients. *Blood Cancer J*. 2017 Dec;7(12):662.
- 10 Barbui T, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia*. 2018 May;32(5):1057–69.
- 11 Barbui T, De Stefano V, Falanga A, Finazzi G, Martinelli I, Rodeghiero F, et al. Addressing and proposing solutions for unmet clinical needs in the management of myeloproliferative neoplasm-associated thrombosis: A consensus-based position paper. *Blood Cancer J*. 2019 Aug;9(8):61.