

Polycythemia vera and essential thrombocythemia of intermediate-age: A real-life, multicenter analysis of first-line treatment approach

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Abstract

Background. The treatment of patients with polycythemia vera (PV) and essential thrombocythemia (ET) is conducted according to well-defined risk stratification systems. We hypothesized that adherence to the guidelines, namely the decision to refrain from introducing cytoreduction in non-high-risk patients, is particularly difficult in patients diagnosed when they are between 40 and 59 years of age (intermediate-age group).

Objectives. To evaluate the group of intermediate-age PV and ET patients, focusing on a first-line treatment approach adapted at diagnosis.

Materials and methods. The study group consisted of 308 PV and ET patients recruited from 6 Polish Adult Leukemia Group (PALG) Centers. Patients were analyzed with respect to disease phenotype, risk group, treatment approach, cardiovascular (CV) risk factors, and occurrence of bleeding or thrombosis.

Results. Overall, 74% of patients in the study group were started on cytoreduction at diagnosis, including 70% of the low-risk PV patients and 85–89% of the non-high-risk ET patients. Factors influencing the decision to start the treatment included higher hemoglobin (Hb) concentration (in PV) as well as higher platelet (PLT) count, and the presence of CV risk factors (in ET). Introducing cytoreduction at diagnosis had no impact on thrombotic events. Patients harboring CV risk factors experienced a higher incidence of complications both at diagnosis and follow-up, independently of the treatment strategy.

Conclusions. We underline the low adherence to recommendations in the treatment of intermediate-age PV and ET patients. Moreover, we emphasize the importance of CV risk factors and stress their impact on disease phenotype in this patient population.

Key words: cardiovascular risk, essential thrombocythemia, cytoreduction, polycythemia vera

Background

Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms (MPN) in which the treatment is aimed at preventing disease-specific complications and reducing the risk of progression. During the course of the disease, with respect to the general population, patients with PV and ET are exposed to an increased rate of thrombotic and bleeding events, and, as a consequence, the treatment recommendations are designed to help mitigate the risk of those complications.^{1,2} Additionally, a small proportion of patients will manifest progressive disease and experience the transformation of phenotype to secondary myelofibrosis or acute leukemia, which directly translates into a dismal prognosis.^{3,4} To date, numerous treatment approaches have become available for patients with PV and ET, and these range from observation only, through phlebotomy and antiplatelet therapy, to a variety of cytoreductive agents. Before establishing the treatment plan in newly diagnosed patients, several factors, including age, cardiovascular (CV) risk, history of thrombosis, and mutational profile, must be considered in order to attribute patients to the specific risk group. Nevertheless, the greatest dilemma concerns the time at which cytoreduction should be started. There are well-defined guidelines supporting the decision to start cytoreductive treatment (CTR) in ET or PV patients above 60 years of age.¹ However, in patients below 40 years of age, cytoreduction is performed more rigorously due to the expected marginal risk of thrombosis along with the possible long-term consequences associated with prolonged exposure to cytoreductive agents, including, but not limited to, secondary neoplasms.⁵ However, considering both the literature as well as their own observations, physicians often struggle with the decision regarding the most appropriate treatment strategy in patients aged 40–59 years, i.e., the intermediate-age group. Patients from the intermediate-age group are still considered low-risk if they had no prior thrombotic event. On the other hand, data from population-based studies suggest an accumulation of CV risk factors in this patient population, along with an impact on overall survival (OS), which may stimulate the decision to introduce cytoreduction.⁶ It remains unclear whether the earlier introduction of cytoreductive therapy in the intermediate-age group results in a lower rate of complications, slower disease progression and better OS.

Objectives

In the current study, we aim to analyze the intermediate-age patients diagnosed with PV or ET and demonstrate real-life based observations regarding adherence to the guidelines and treatment approaches adapted at diagnosis.

Materials and methods

Data source

This retrospective study was performed on behalf of the Polish Adult Leukemia Group (PALG). Six PALG Centers in Poland were invited to participate in the study. Study participants were selected on the basis of a study-specific data questionnaire received from the participating Centers.

Study population and variables of interest

Adult patients diagnosed with PV or ET between 2000 and 2022, in whom the diagnosis was established between 40 and 59 years of age, were identified as potential candidates for inclusion in the study group. Only patients alive at the study time, with available full clinical data regarding investigated variables and meeting the myeloproliferative neoplasms (MPN) World Health Organization (WHO) 2016 criteria for PV or ET, apart from triple-negative ET patients ($n = 20$), were considered.⁷

The study focused on the treatment approach used at diagnosis, specifically whether the patient underwent cytoreduction or not. Additional variables included demographic data, laboratory values at diagnosis, molecular profile, presence of CV risk factors, and thrombotic complications recorded at diagnosis or follow-up. Extreme thrombocytosis was defined as platelet (PLT) count >1000 G/L (ExT1000) or >1500 G/L (ExT1500). The molecular profile was established by screening for the presence of *JAK2V617F*, *JAK2* exon 12, *CALR*, and *MPL* mutations.^{8–10} Patients in whom none of those mutations had been detected were labeled as *JAK2*-negative or triple negative (TN) for PV and ET patients, respectively. Cardiovascular risk factors included arterial hypertension, hypercholesterolemia, diabetes mellitus, obesity, and smoking. Thrombotic events included myocardial infarction (MI), ischemic stroke (IS), deep vein thrombosis (DVT), splanchnic vein thrombosis (SVT), central nervous system (CNS), and arterial thrombosis (AT).

Risk group

The collected data were used to assign patients to the risk groups in accordance with current European Leukemia Network (ELN) recommendations: PV patients were evaluated with a conventional prognostic system, whereas ET patients with the use of the IPSET-thrombosis (IPSET-T) system and the revised IPSET-thrombosis (rIPSET-T) criteria proposed by Barbui et al. in 2015.^{1,11,12} The collected data were used to characterize the study population and to further characterize patients with and without cytoreduction.

Statistical analyses

Statistical analysis was performed to screen for significant differences between groups. Calculations were done

using Statistica v. 13.3 (StatSoft, Tulsa, USA). Data were statistically described in terms of median and range. Since none of the analyzed variables showed normal distribution, a comparison between the 2 groups was performed using the Mann–Whitney U (MWU) test for continuous variables and the χ^2 test for categorical variables.

Univariable and multivariable logistic regression models were built to test associations between the introduction of CTR and independent variables of interest for PV and ET group separately. Collected data were analyzed to search for factors possibly influencing the decision to introduce CTR. Sex, presence of CV risk factors, ExT1000, mutational status, and presence of thrombosis (as qualitative variables) followed by age, hemoglobin (Hb) concentration, PLT, and white blood cells (WBC) count (as qualitative variables) were considered for the inclusion in the model. Given that we revealed that CTR is introduced independently of the risk group, variables used to calculate the risk – presence of thrombosis and mutational status – were not included in the model. Moreover, since all PV patients with ExT1000 were started with cytoreduction, ExT1000 was not used in the PV group. In summary, sex, presence of CV, ExT1000, age, Hb concentration, PLT, and WBC count were retained in the model. Only variables showing statistical significance in univariable analysis were analyzed in multivariable analysis. Linear relationships of dependent variables with quantitative variables included in the regression model were checked. P-values in the likelihood ratio test were >0.05 for all quantitative variables (Hb in PV and PLT in ET). Multicollinearity was statistically significant for WBC and PLT count in the ET group ($p < 0.05$) and Hb and WBC count in the PV group ($p < 0.05$). Only PLT count in the ET group was retained in the multivariable regression model. Since Hb concentration was the only variable showing statistical significance in the PV group, no multivariable model was created. In ET, the multivariable regression model was built using a backward stepwise approach with cross-validation. The analysis ended at the 4th step. Out of 3 previously statistically significant variables, PLT count has been eliminated from the model, with only CV and ExT1000 being retained as independent variables. Pseudo R^2 for each logistic regression model and multivariable model was calculated using the Cox–Snell formula. P-values were considered significant when $p < 0.05$.

Results

The final study group consisted of 308 representative patients diagnosed with PV or ET in the intermediate-age bracket. The median time from the diagnosis to this analysis was 11 years (range 0–22 years).

Cytoreductive treatment was introduced at diagnosis in 227 (74%) patients (Table 1). The most frequently used cytoreductive agent was hydroxyurea (HU) ($n = 211$), followed by anagrelide ($n = 8$) and busulfan ($n = 8$). No patients

Table 1. General characteristics of the study group

Diagnosis	PV	ET
n	119	189
Age, median (range) [years]	52 (40–59)	52 (40–59)
Sex, F/M	56/63	125/64
Parameters at diagnosis, median (range)		
Hb [g/dL]	17.8 (14.8–23.1)	14 (10.6–16.4)
Hct [%]	53.7 (45.9–72.0)	42 (28.6–48.5)
PLT [G/L]	421 (130–1630)	835 (455–2638)
WBC [G/L]	9.6 (4.92–21.12)	8.6 (3.0–25.9)
LDH [U/L]	230 (134–426)	219 (59–651)
EPO [mU/mL]	2.2 (0.6–40)	6.8 (1–120)
Mutational status, n (%)		
JAK2V617F	97 (81.6)	119 (63)
CALR	N/A	33 (17.4)
MPL	N/A	6 (3.2)
TN	N/A	20 (10.6)
Ex12	0 (0)	N/A
JAK2-negative	22 (18.4)	11 (5.8)
ExT1000 (%)	5 (4.2)	62 (32.8)
ExT1500 (%)	1 (0.8)	9 (4.8)
Hb >20 g/dL (%)	23 (19.3)	0
Hct $>55\%$ (%)	47 (40)	0
WBC >15 G/L (%)	12 (10)	5 (2.6)
CV risk factors (%)	63 (52.9)	97 (51.3)
Treatment		
Cytoreduction (%)	91 (76.5)	136 (72)
Phlebotomy (%)	60 (50.4)	N/A
Antiplatelet/anticoagulant (%)	85 (71.4)	159 (84.1)
Complications at diagnosis, n (%)	24 (20.2)	37 (19.6)
MI	5 (4.2)	9 (4.8)
IS	12 (10)	9 (4.8)
DVT	6 (5)	13 (6.9)
SVT	1 (1)	1 (0.5)
CNS	0	3 (1.6)
AT	0	1 (0.5)
Complications at follow-up, n (%)	10 (8.5)	22 (11.6)
MI	1 (0.8)	6 (3.2)
IS	7 (5.9)	4 (2.1)
DVT	1 (0.8)	6 (3.2)
SVT	0	3 (1.6)
CNS	1 (0.8)	0
AT	0	1 (0.5)

n – number; F – female; M – male; CV – cardiovascular risk; ExT1000 – PLT >1000 G/L; ExT1500 – PLT >1500 G/L; MI – myocardial infarction; IS – ischemic stroke; DVT – deep vein thrombosis; SVT – splanchic vein thrombosis; CNS – central nervous system thrombosis; AT – arterial thrombosis; PV – polycythemia vera; ET – essential thrombocythemia; Hb – hemoglobin; Hct – hematocrit; PLT – platelet count; WBC – white blood cell count; LDH – lactate dehydrogenase; EPO – erythropoietin. Extreme thrombocytosis was defined as platelet (PLT) count >1000 G/L (ExT1000) or >1500 G/L (ExT1500).

received interferon as the first-line therapy. The high-risk group constituted of 24 (20.2%) PV patients and 71 (37.6%) and 37 (19.6%) ET patients when IPSET-T and rIPSET-T were used, respectively (Table 2). In PV, all patients from the high-risk group, along with 67 (70%) patients from the low-risk group, received cytoreduction at diagnosis. In ET, cytoreduction was started in 60 (85%) and 33 (89%)

Table 2. Risk stratification of the study group

Risk	Very low	Low	Intermediate	High
PV	N/A	95 (79.8)	N/A	24 (20.2)
ET (IPSET-T)	N/A	64 (33.8)	54 (28.6)	71 (37.6)
JAK2V617F	N/A	0	51 (42.9)	68 (57.1)
CALR	N/A	30 (91)	2 (6)	1 (3)
ET (IPSET-T revised)	60 (31.7)	92 (48.7)	0	37 (19.6)
JAK2V617F	0	88 (74)	0	31 (26)
CALR	30 (91)	0	0	3 (9)

PV – polycythemia vera; ET – essential thrombocythemia.

Table 3. Results of logistic regression model identifying variables contributing to the introduction of CTR in the study group

Covariate		Univariable analysis				Multivariable analysis			
		OR	95% CI	p-value	pseudo R ²	OR	95% CI	p-value	pseudo R ²
PV	age	1.041	0.97–1.12	0.2645	0.010	–	–	–	–
	female sex	1.017	0.67–1.55	0.9391	0.000	–	–	–	–
	presence of CV	1.186	0.78–1.81	0.4308	0.005	–	–	–	–
	Hb	1.438	1.07–1.92	0.0146	0.058	–	–	–	–
	PLT	1.001	0.99–1.00	0.1599	0.019	–	–	–	–
	WBC	1.133	0.99–1.30	0.0779	0.030	–	–	–	–
ET	age	1.028	0.98–1.08	0.3138	0.005	–	–	–	0.25
	male sex	1.846	0.90–3.78	0.0931	0.016	–	–	–	
	presence of CV	3.406	1.73–6.72	0.0004	0.069	5.025	2.38–10.63	<0.0001	
	Hb	0.891	0.68–1.18	0.4172	0.003	–	–	–	
	PLT	1.004	1.00–1.00	<0.0001	0.133	–	–	–	
	WBC	1.089	0.97–1.22	0.1485	0.012	–	–	–	
	ExT1000	12.771	3.78–42.97	<0.0001	0.147	18.001	5.14–63.06	<0.0001	

PV – polycythemia vera; ET – essential thrombocythemia; CV – cardiovascular risk; OR – odds ratio; 95% CI – 95% confidence interval; Hb – hemoglobin; PLT – platelet count; WBC – white blood cell count; CRT – cytoreductive treatment. Extreme thrombocytosis was defined as platelet (PLT) count >1000 G/L (ExT1000) or >1500 G/L (ExT1500).

high-risk patients but also in 76 (64%) and 103 (68%) patients from the non-high-risk group according to IPSET-T or rIPSET-T, respectively (Fig. 1).

Covariables with possible influence on the tendency to start cytoreduction were investigated in the logistic regression model created independently for the PV and ET groups. In the univariable analysis, only a higher Hb concentration was identified as a factor contributing to the introduction of CTR in PV patients ($p = 0.015$). For ET patients, the presence of CV risk factors ($p = 0.001$), ExT1000 ($p < 0.001$) and higher PLT count ($p < 0.001$) were identified as factors contributing to the introduction of CTR. In the multivariable analysis, ExT1000 and CV risk retained their significance. The results of this analysis are presented in Table 3.

To further investigate patients who were started with cytoreduction, despite being in the non-high-risk group, an additional comparative analysis, employing the variables indicated in the regression model, was performed in the non-high-risk patients only. Here, low-risk PV patients who started with CTR had a higher Hb concentration with respect to patients without cytoreduction

(median 18.2 g/dL compared to 17.5 g/dL; $p = 0.027$; MWU; $U = 667$). Non-high-risk ET patients receiving cytoreduction had a higher PLT count (median 980 G/L compared to 720 G/L; $p < 0.001$; MWU; $U = 1178.5$) and more frequently had ExT1000 (47.6% compared to 6%; $p < 0.001$; χ^2) or CV risk factors (49.5% compared to 26.5%; $p = 0.007$; χ^2) than patients not started with CTR. Those findings further underline that the decision to start cytoreduction was independent of the risk group.

Subsequently, patients with and without thrombotic complications at follow-up were compared regarding the variables identified as contributing to introducing cytoreduction in order to examine whether starting the treatment early translates to outcomes. The incidence of thrombosis at follow-up was 6/91 (7%) and 18/136 (13%) in patients with cytoreduction and 4/28 (14%) and 4/53 (8%) in patients without cytoreduction in the PV ($p = 0.372$; χ^2) and ET ($p = 0.399$; χ^2) groups, respectively. There were no differences in the baseline median PLT count (872 G/L compared to 828 G/L; $p = 0.270$; MWU; $U = 1570.5$ for ET and 581 G/L compared to 414 G/L; $p = 0.294$; MWU; $U = 435$ for PV) and median Hb concentration (14.2 g/dL compared to 14.0 g/dL,

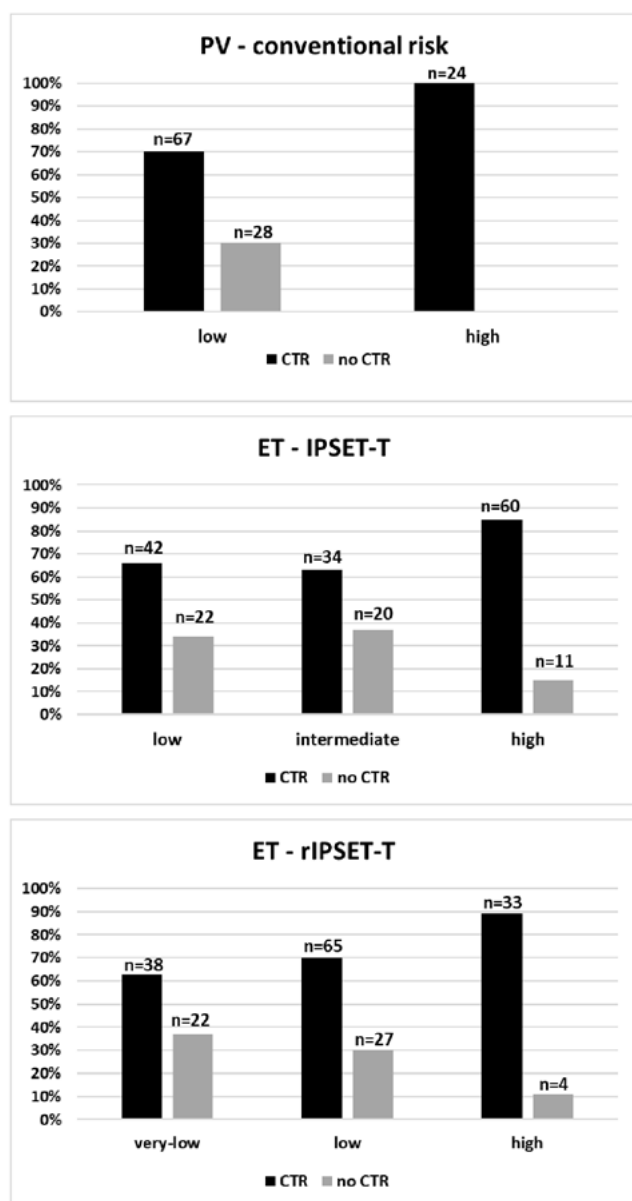


Fig. 1. The number of patients who received CTR among the risk groups

PV – polycythemia vera; ET – essential thrombocythemia;
CTR – cytoreductive treatment.

$p = 0.932$, MWU; $U = 1816$ for ET and 17.9 g/dL compared to 17.8 g/dL; $p = 0.807$; MWU; $U = 519$ for PV) in patients experiencing thrombosis as compared to patients without complications, respectively. Similarly, the distribution of CV risk factors was comparable among patients with (12/22; 54%) and without (85/167; 51%) thrombosis in the ET group ($p = 0.748$; χ^2). In the PV group, CV risk factors were present in 10/10 (100%) patients who developed complications and only in 53/109 (48%) patients without complications ($p = 0.005$; χ^2). However, those findings must be considered with caution given that the study group did not comprise consecutive patients and only the data regarding the first-line therapy were collected.

As an exploratory objective, we investigated the relationship between the presence of CV risk (evaluated

at diagnosis) and the incidence of thrombosis (at diagnosis). In PV, 20/24 (83%) patients who had experienced complications at diagnosis had already harbored CV risk factors, compared to only 43/95 (45%) patients without complications at diagnosis ($p = 0.002$; χ^2). Similarly, in ET, 33/37 (89%) patients who had experienced complications at diagnosis had had CV risk factors, compared to 64/152 (42%) patients without complications at diagnosis ($p < 0.001$; χ^2).

Discussion

In this study we performed a retrospective evaluation of the real-world trends in the treatment of 308 Polish patients diagnosed with ET and PV in the age range of 40–59 years (intermediate-age group). The study revealed a higher-than-expected willingness to adopt the approach of introducing cytoreductive therapy at diagnosis in the evaluated patients. According to the Philadelphia-negative MPN management recommendations provided by the ELN, patients with PV should be stratified into risk groups depending on age and presence of prior thrombosis, whereas risk stratification in patients diagnosed with ET should be based on the IPSET-T or rIPSET-T system.^{1,11–14} Recently, novel stratification systems incorporating genomic data were developed for PV and ET (MIPSS-PV and MIPSS-ET) to better assess the risk of progression to AML or MF.¹⁵ While it is indisputable that, in the future, every patient should be evaluated from a cytogenetic and molecular standpoint, those assessments are inaccessible in everyday clinical practice in the majority of centers worldwide. Nevertheless, regardless of the diagnosis and stratification system, cytoreduction is recommended only for high-risk patients. In the analyzed population, the majority of patients were assigned to the non-high-risk group and nevertheless started with cytoreduction at diagnosis. These findings raise a question about the adherence to and usefulness of the aforementioned recommendations. When physicians easily recognized high-risk patients, refraining from starting treatment in the non-high-risk group appeared to be a challenge and trends of overtreatment could also be found among other studies. In a study evaluating a young ET group (age 18–39 years), among 192 patients (12% in the high-risk group), as many as 107 (55%) received CTR.¹⁶ Similar results were obtained from the analysis of an entire population of young low-risk ET patients (age 18–59 years), where cytoreduction was started in 170 (51%) of patients.¹⁷ In a recent real-world study focused on young patients with a diagnosis of MPN, a total of 444 patients (median age of diagnosis 20.4 years, range 2–25 years) from multiple European centers were evaluated.¹⁸ During a median follow-up of 9.7 years, cytoreduction was introduced in 301 (67.8%) of evaluated patients. However, the authors underline that only 21.4% of patients were strictly eligible to receive cytoreduction according to guidelines. In light of this, it is important

to determine what, if not the recommendations, is a driving factor for introducing CTR in our intermediate-age group. Through the construction of a logistic regression model, we revealed that a higher Hb concentration in PV and the presence of CV risk factors and ExT1000 in ET patients were variables contributing to the introduction of CTR. The confirmation of those findings was limited to the non-high-risk group. The results suggest that extreme laboratory values and comorbidities may be perceived as indicators for initiating therapy.

In regard to PV, the decision to introduce cytoreduction may be more understandable than in ET. Even young patients with PV are exposed to a higher risk of thromboembolic complications with respect to ET.¹⁹ Additionally, a recent publication showed that the cumulation of CV risk factors in PV patients, independent of age, has a negative impact on OS.²⁰ Treatment recommendations underline that all patients with PV, regardless of age, should receive phlebotomy to reduce hematocrit (Hct) below 45%, based on the results of the CYTO-PV trial.²¹ However, the risk of symptomatic iron deficiency and logistic problems in real-life settings encourages the physician to introduce cytoreduction, even in low-risk patients, as a more reliable approach to managing Hct and minimizing the possibility of complications. Therapeutic dilemma in low-risk PV is debated.^{22,23} On the other hand, the justification for introducing cytoreduction in ET patients is not as understandable. Findings similar to those presented in this study have been observed for young patients with ET, with 1 study highlighting that cytoreduction is given willingly in patients with ExT1000, despite a comparable distribution of CV risk factors and lower incidence of AT.¹⁶

Recently, Abu-Zeinah et al. presented a database analysis of 40,333 MPN patients followed between 2001–2017. The authors confirmed higher mortality in young PV and ET patients in comparison to the healthy population of the same age. Furthermore, the study revealed a significantly higher excess of all-cause mortality in young (<60 years of age) MPN patients with respect to the older (≥60 years of age) population of MPN patients.²⁴ The authors indicate that this excess mortality may be the result of undertreatment within the group of young and potentially low-risk patients with MPNs. However, those observations are based on a database analysis that does not include the data regarding treatment, with the assumption that patients are treated strictly according to the guidelines. If findings from our study could be extrapolated to worldwide practice, and similar trends shown in numerous studies suggest that they could, this higher excess mortality may not be a result of undertreatment but rather overtreatment or improper treatment. In both our study groups and in the literature, HU is the most frequently used cytoreductive agent.^{16,17,20} There is an abundance of warnings regarding the use of HU in younger patients, resulting mainly from uncertainty concerning its leukemogenicity and the possibility of the development of a second malignancy.^{5,25} This threat

was further acknowledged by Abu-Zeinah et al. in their study of excess mortality, where the authors reported an unacceptably high degree of cancer death in young patients with MPNs.²⁴ Nonetheless, each patient should be evaluated individually, and if the physician qualifies for cytoreduction, the use of different agents needs to be considered. Anagrelide is a potent cytoreductive agent available as a second-line treatment for patients with ET.²⁶ However, reports of inducing bone marrow fibrosis should be taken into consideration.²⁷ Alternatively, ruxolitinib is an attractive therapeutic option for symptomatic patients with PV. However, its use is limited to patients with confirmed refractoriness to HU.^{28,29} Finally, peg-IFN and ropeg-IFN represent the best alternatives for PV and ET patients, allowing them to limit the hazards of extended cytoreduction, avoid exposure to iron deficiency, achieve molecular remissions, and possibly prolong OS.^{30–36} Nevertheless, due to limited accessibility, none of our patients were treated with the use of this agent as the first-line therapy.

We revealed that the occurrence of thrombotic complications was independent of introducing CTR, Hb concentration and PLT count at diagnosis in both the ET and PV groups. These findings suggest that the rationale for an early start of cytoreduction, based on extreme laboratory values, might not modify the disease course. On the other hand, the study conducted on the European general population highlighted that, starting from the age of 40, there is an increasing impact of CV risk factors on survival.⁶ In our study group, patients with CV risk factors constituted 52% of the study population. When compared to young ET patients, where only 26% harbored CV risk, it is apparent that CV burden increases exponentially within intermediate-age group.¹⁶ An exploratory finding from our study showed that almost all patients who had experienced complications at diagnosis presented CV risk factors (83% of PV and 89% of ET patients), while all PV patients who developed complications post diagnosis also harbored CV risk factors at diagnosis. In the aforementioned study by Abu-Zeinah et al., excess mortality from CV events was significantly higher only in PV patients.²⁴ Considering those observations, the importance of evaluating CV risk should be emphasized and may indicate treatment introduction in the intermediate-age group.

Limitations

The study's main limitation is its retrospective nature. However, it was conducted in a multicenter setting and included a relatively large patient population. The study focuses on the data regarding the first-line treatment approach and does not evaluate follow-up treatment.

The study group consists of patients who were alive at the time the study was conducted, hence does not include patients who were deceased as a result of thrombosis, bleeding or disease evolution. This exclusion does not affect the study's findings.

Conclusions

In this study, we revealed that cytoreduction is used in excess when confronted with the guidelines in intermediate-age patients diagnosed with ET and PV. Based on our findings, it remains to be seen whether starting cytoreduction in young patients is reasonable, given that it does not translate into a reduced incidence of disease-specific complications. Patients with ET and PV, regardless of age, are a heterogeneous group. Therefore, multiple factors, possibly yet undiscovered, contribute to disease phenotype. Moreover, we underlined that the presence of CV risk factors also plays a significant role in patients below 60 years of age, emphasizing the idea of pursuing individualized treatment approaches.











Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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