



Impact of platelets on major thrombosis in patients with a normal white blood cell count in essential thrombocythemia

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Abstract

Objectives: Cell counts have a significant impact on the complex mechanism of thrombosis in patients with essential thrombocythemia (ET). We recently demonstrated a considerable impact of white blood cell (WBC) counts on thrombotic risk in patients with optimized platelet counts by analysing a large anagrelide registry. In contrast, the current analysis of the registry aimed to estimate the influence of platelet counts on thrombotic risk in patients with optimized WBC counts.

Methods: Cox regression analysis and Kaplan-Meier plot were applied on all patients in the registry with optimized WBC counts.

Results: By using the calculated cut-off of 593 G/L for platelets, Cox regression analysis revealed a clear influence of elevated platelet counts on the occurrence of a major thrombotic event ($P < .001$). A Kaplan-Meier plot revealed a markedly shorter time to a major thrombotic event for patients with platelet counts above the cut-off ($P < .001$).

Conclusions: The data show clear impact of platelet lowering on the thrombotic risk in ET patients with normal WBC counts. Therefore, selective platelet lowering with anagrelide appears sufficient for thrombotic risk reduction in WHO-diagnosed ET patients lacking leukocytosis.

KEYWORDS

essential thrombocythemia, platelets, thrombotic risk, white blood cells

Veronika Buxhofer-Ausch and Heinz Gisslinger contributed equally.

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1 | INTRODUCTION

Thromboembolic complications are prevalent in essential thrombocythemia (ET). A recent meta-analysis including 13 436 patients with classical MPNs revealed a pooled prevalence of overall thrombosis in 20.7% of newly diagnosed patients with ET.¹ Moreover, a population-based cohort study including 9429 patients with MPNs and 35 820 control participants confirmed highest rates of thromboembolic complications shortly after diagnosis, but thrombosis hazard ratios were also markedly increased at later time points compared to the control group.² Pathogenesis of thrombosis in myeloproliferative neoplasms is considered very complex and not fully elucidated.³ In addition to the traditional risk factors, advanced age and past history of thrombosis,⁴ the mutational profile,⁵ inflammation,³ novel mechanisms including abnormal cell adhesion and formation of neutrophil extracellular traps,⁶ blood cell counts are also supposed to contribute significantly to the thrombotic risk in MPNs.³ A recent meta-analysis including more than 30 000 patients reported an association between leukocytosis and thrombosis in ET.⁷ Despite guidelines for the management of ET that suggest normalization of platelet and white blood cell (WBC) counts,⁸ several retrospective studies could not prove a benefit from achievement of a complete haematological response.^{9,10} However, there are several studies including two large randomized trials that demonstrate a significant positive effect of platelet lowering on the thrombotic risk, especially in WHO-diagnosed ET patients.¹¹⁻¹³ We took the opportunity to analyse the Austrian part of a large anagrelide registry which allows observing blood counts and efficacy of treatment under real-life conditions and with long follow-up. At first, we investigated the combined impact of WBC cells and platelet counts on the thrombotic risk in ET.¹⁴ Subsequently, we analysed the influence of WBC on thrombotic risk in patients with optimized platelet counts.¹⁵ The purpose of the current study was to complement these analyses by investigating the impact of platelet counts on thrombotic risk in patients with optimized WBC counts.

2 | PATIENTS AND METHODS

All patients of the registry who had a median leucocyte count until end of observation or date of major thrombotic event (MTE) below the calculated cut-off of 9.66 G/L, which was previously found to be relevant for an increased rate of thrombosis,¹⁵ were considered for this analysis. Inclusion criteria consisted of a valid diagnosis of ET according to PVSG or WHO criteria, the availability of WBC values and a follow-up time of at least 5.64 months (shortest time until MTE occurrence). Registry entry was the start of treatment with anagrelide (Thromboreductin® AOP Orphan). Observation ended with the closure of the data file or with MTE occurrence. Concurrent treatment with aspirin and other concurrent cytoreductive treatment were at the discretion of the treating physician. Considered fatal and non-fatal major thrombotic events included stroke, transitory ischaemic attack, myocardial infarction, coronary artery disease/

Novelty statement

- Platelets lowering in ET reduces the thrombotic risk.
- Elevated platelet counts in ET enhance the risk of thrombosis despite normal white blood cell counts.
- Selective platelet lowering seems sufficient in WHO-diagnosed ET without leucocytosis.

angina pectoris, peripheral arterial disease, deep vein thrombosis, pulmonary infarction/embolism and splanchnic vein thrombosis/Budd-Chiari syndrome. The repeated measures of platelet and WBC counts were both condensed by calculation of medians (median). The suitability of thrombocyte and WBC median for the prediction of major thrombotic events was checked by means of receiver operating characteristic curves (ROC); cut-offs were assessed by the Youden index. The cut-off for the platelet median (540.5 G/L) was also used for the definition of subgroups. Cox regression was used to investigate the influence of the following covariates on the occurrence of major thrombotic event (MTE): age at end of observation or date of MTE, WBC median until end of observation or date of MTE > / ≤ 8.48 G/L, platelet median until end of observation or date of MTE > / ≤ 593.0 G/L. All data of continuous variables were checked for normal distribution (test of normality: Kolmogorov-Smirnov with Lilliefors significance correction, type I error = 10%). Variables with normally distributed data were compared between subgroups by the t test for independent samples (test for variance homogeneity: Levene test, type I error = 5%); otherwise, the exact Mann-Whitney U test was used. Categorical variables were compared by Fisher's exact test. Time to MTE, depicted by Kaplan-Meier plots, was compared by the log rank test. The type I error was not adjusted for multiple testing. Therefore, the results of inferential statistics are descriptive only. Statistical analysis was performed using the open-source R statistical software package, version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the local Ethics Committee and conducted in accordance with the current version of the Helsinki Declaration.

3 | RESULTS

The original registry included 845 patients, 309 of which fulfilled all inclusion criteria for this analysis and displayed a median WBC count of <9.66 G/L during the whole follow-up period. Follow-up in the included patients is 4.47 [2.40; 6.97] years, corresponding to 18 372 patient months or 1531 patient-years, respectively. The majority (95%) of patients were primarily classified or later reclassified according to the WHO classification system (before 2008 according to WHO 2001 and after 2008 according to WHO 2008, respectively). In the remaining, 5% of patient's information about the applied classification system is missing. 192 patients (62.1%) were females. Median patients' age at time of study entry was 59.32 [49.43; 68.86]



years. Median platelet count at entry into the register was 757.00 [545.00; 954.00] G/L, and median WBC count at study entry was 7.7 [6.10; 8.90] G/L. Median platelet count of the entire cohort during the time of observation (until major event or end of follow-up) was 475.00 [397.50; 570.00] G/L, and median WBC count was 7.50 [6.30; 8.45] G/L. Eleven patients (3.56%) experienced at least one major arterial or venous event until data analysis, corresponding to 0.72 events per 100 patient-years. Time to first major event was median 2.75 [0.80; 4.25] years. Age of patients at their first major event was 65.13 [56.07; 81.56] years compared to 65.02 [54.70; 72.97] years at the end of observation period in patients without any major event ($P = .48$). The median platelet count until end of observation (in patients without an event) was 473.75 [395.00; 560.50] G/L and 597.00 [543.00; 660.00] G/L in those patients with an event, respectively, thus differing considerably ($P = .018$) between the two groups. The median WBC counts until the first thrombotic event or until end of observation (in patients without an event) showed no difference with 8.70 [6.30; 9.30] and 7.48 [6.30; 8.40] G/L, respectively ($P = .14$).

By using the calculated (Youden index) cut-off of 593 G/L for platelet counts, major thrombotic events are more frequent in the group of patients with median platelet counts above the cut-off ($P = .019$). Comparison of patients' characteristics with platelet counts below and above the calculated cut-off of 593 G/L, respectively, is depicted in Table 1.

In the three patients with thrombotic events who belonged to the group with platelet counts below the calculated cut-off of 593 G/L, the individual platelet counts immediately before a major event ranged between 176 and 495 G/L. However, in all eight patients with thrombotic events who belonged to the group with platelet counts above the calculated cut-off of 593 G/L, the individual

platelet counts immediately before a major event ranged between 383-930 G/L (data not shown).

Cox regression analysis revealed a clear influence of elevated platelet counts above the Youden index-derived cut-off of 593 G/L ($P < .001$) on the occurrence of a MTE. From the other investigated covariates, age at time of an event or end of observation was statistically inconspicuous, while WBC counts above the Youden index-derived cut-off of 8.48 G/L (but below 9.66 G/L as defined by the exclusion criteria) exhibited a clear influence on the occurrence of a MTE ($P = .028$) (Figure 1).

A Kaplan-Meier estimator was applied and revealed a markedly shorter time to a major thrombotic event for patients who display platelet counts >593 G/L compared to patients with platelet counts ≤ 593 G/L ($P < .001$) (Figure 2).

4 | DISCUSSION

Our analysis proves the importance of PLT lowering on frequency of MTE in anagrelide-treated ET patients with normal WBC counts. Furthermore, a sustained elevation of PLT counts above the calculated threshold level of 593 G/L during follow-up is linked with a markedly higher risk of MTE and a clearly shorter time to a MTE despite median WBC counts below 9.66 G/L. The lowest rate of MTE can be achieved with PLT counts below 593 G/L and WBC counts below 8.48 G/L during follow-up. These data nicely complement our previous analyses of data from the same registry. In 2016, we performed an analysis of the whole cohort of 620 patients with the aim of assessing the influence of platelet and WBC counts on the risk of major thrombotic events. Using the calculated cut-offs of 574.5 G/L for platelets and 8.48 G/L for WBC, respectively, the Cox regression

TABLE 1 Patient characteristics according to platelet counts

Variable		Patients with PLT > 593; n = 65	Patients with PLT ≤ 593; n = 244	P- value
FU	Years, median (quartiles)	3.01 (1.46; 5.26)	4.76 (2.87; 7.52)	<.001
Gender	Female, n (%)	42 (64.6)	158 (64.8)	>.999
	Male, n (%)	23 (35.4)	86 (35.2)	
Age at study entry	Years, median (quartiles)	58.23 (48.50; 69.83)	59.47 (49.68; 68.85)	.696
Age at MTE or last FU	Years, median (quartiles)	63.62 (53.82; 72.15)	65.33 (54.99; 73.15)	.249
WBC at MTE or last FU	G/L, median (quartiles)	7.40 (6.40; 8.75)	7.40 (6.10; 8.70)	.846
WBC until MTE or last FU	G/L, median (quartiles)	7.70 (6.80; 8.90)	7.40 (6.20; 8.30)	.022
WBC median until MTE or last FU	>8.48 G/L, n (%)	23 (35.4)	53 (21.7)	.034
	≤8.48 G/L, n (%)	42 (64.6)	191 (78.3)	
JAK2V617F ^a	Positive, n (%)	4 (28.6)	36 (54.5)	.139
	Negative, n (%)	10 (71.4)	30 (45.5)	
MTE	n (%)	8 (12.3)	3 (1.2)	<.001

Abbreviations: FU, Follow-up; MTE major thrombotic event; WBC white blood cells.

^aInformation on JAK2 Status available in 80 patients.

A P-value of ≤ 0.05 was considered as statistical significant.

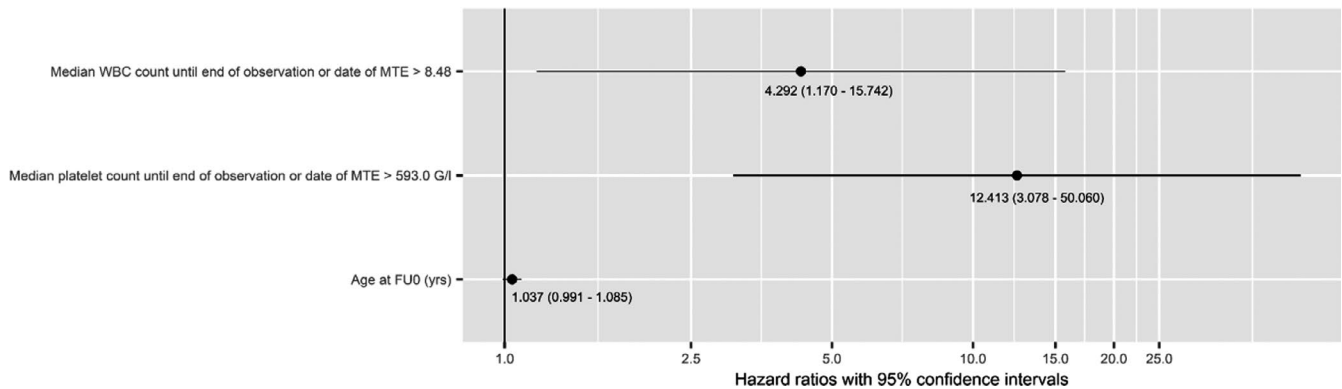


FIGURE 1 Median WBC count until end of observation or date of MTE ≥ 8.48 G/L but ≤ 9.66 G/L. MTE, major thrombotic event

Kaplan-Meier Plot

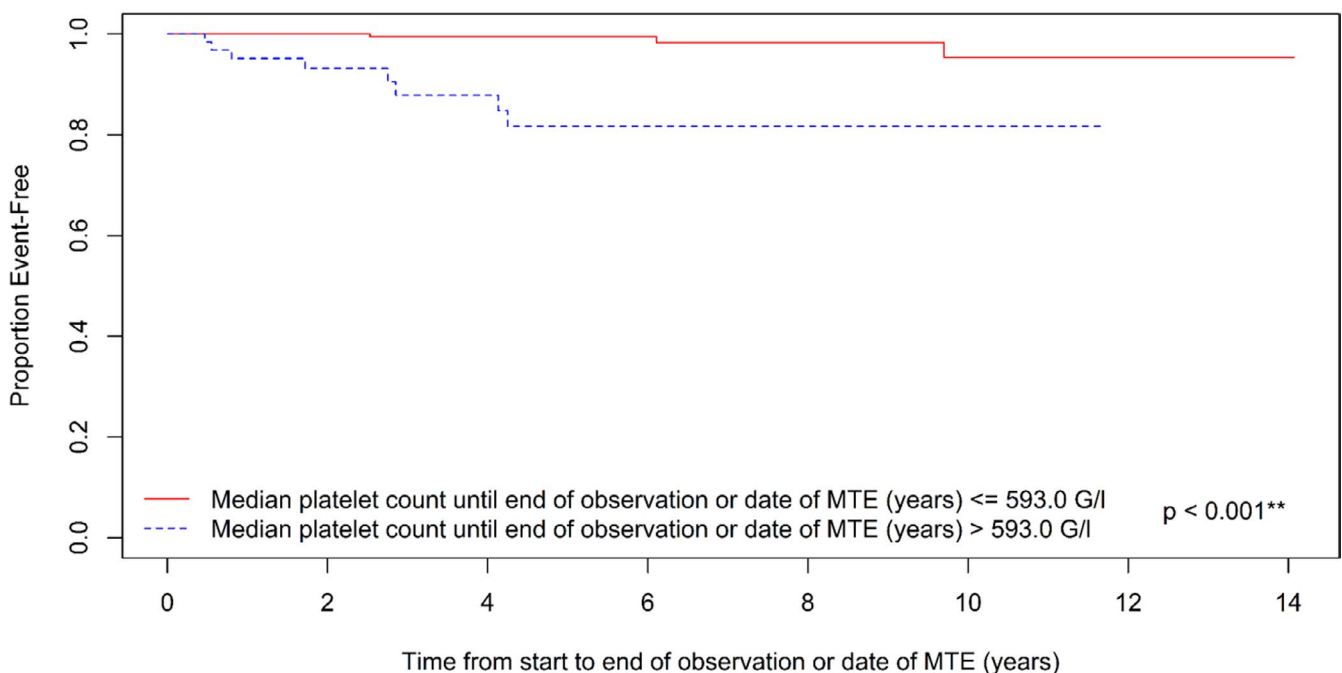


FIGURE 2 Subgroup comparison by Kaplan-Meier Plot analysis. Patients who display platelet counts above 593 G/L have a markedly shorter time to a major thrombotic event compared to patients with platelet counts below 593 G/L [Colour figure can be viewed at wileyonlinelibrary.com]

analysis revealed a considerable influence of elevated platelets ($P = .008$) and WBC counts ($P = .011$) on the occurrence of a thrombotic event. Moreover, our former analysis indicated an interaction of certain platelet and WBC counts by showing time to a major thrombotic event was shortest ($P < .001$) and frequency-related 100 patient-years was highest ($P < .001$) when both platelet and WBC counts ranged above the calculated cut-offs.¹⁴ In order to identify the impact of WBC on the thrombotic risk in patients with optimized platelet counts below the earlier calculated cut-off of 574.5 G/L, we performed another analysis within the registry and identified a cut-off of 9.66 G/L for WBC as statistically relevant ($P = .12$). This result points to the importance of additional correction of elevated WBC counts even if platelet counts are already optimally managed.¹⁵ The

recent analysis highlights the reverse situation, namely the impact of platelet counts in patients with optimized WBC counts. Since WHO-classified patients are very likely displaying normal WBC counts, these data highlight the importance of a platelet-lowering therapy in WHO-diagnosed ET. Moreover, the data support the sufficiency of an exclusively platelet-lowering strategy in patients with normal WBC counts in patients with ET.

There have been several attempts to define an appropriate target value for platelets in ET. Despite the proven benefit of cytoreductive treatment on vascular complications, no particular threshold was shown to be more protective against thrombosis.¹⁶ Although several retrospective studies could not prove a benefit from achievement of a complete platelet response,^{9,10} former and



also current guidelines recommend normalization of the platelet count.^{8,17} However, in most of the performed studies, the correlation between follow-up platelet counts and thrombotic events was not investigated. A recent analysis of the Czech part of the registry revealed a higher platelet count prior to a thrombotic event compared to time points without an event (454 G/L vs 400 G/L) despite a lack of any prognostic value of platelet counts at diagnosis.¹⁸ In our registry cohort, the clinical impact of median platelet counts during the course of the disease and median platelet counts to a greater or lesser extent directly prior to a thrombotic event was comparable (data not shown). Pretreatment prior to registry entry and lack of diagnostic data preclude a comment on the importance of platelet count at diagnosis in our cohort. However, the results of the Czech registry analysis definitely support our observation of the importance of elevated platelet counts during the course of the disease on the risk of major thrombosis.

We have recently analysed the registry with regard to application of anagrelide in older age groups. We found good tolerability and satisfying efficacy across all age groups (Buxhofer-Ausch et al, manuscript in preparation) supporting earlier observations.^{19,20} Broad usage of hydroxyurea in patients with MPN is discussed controversially due to a possible leukemogenic effect.^{21,22} A recent publication on almost 3500 patients treated with hydroxyurea and/or anagrelide reported cases of secondary leukaemia only in the patients with hydroxyurea exposure but none in the patients with sole anagrelide treatment.²³ As long as an association is not definitely disproved (large prospective, controlled studies with long follow-up would be necessary), we should be very cautious with the prescription of hydroxyurea, especially in younger patients. In younger patients with ET, interferon compounds are a reasonable alternative with the addition of a potentially disease-modifying effect.^{24,25} This is especially of importance in the light of a significantly reduced life expectancy in patients with ET, even if not as pronounced as in polycythemia vera or primary myelofibrosis.²⁶ Therapy with interferon is also a safe option in pregnancy as several reports prove.^{27,28} A recently published meta-analysis, which also included our first registry investigation,¹⁴ proved leukocytosis as risk factor for arterial thrombosis in ET.⁷ In the same year, an analysis of a Croatian cohort also identified leukocytosis as risk factor for arterial thrombosis. The calculated cut-offs predicting a higher risk of thrombosis were 9.2 G/L for WBC and 632 G/L for platelets, respectively.²⁹ We are certainly aware of the limitations of our registry analyses due to potential incompleteness of data and also multiple testing, which allows conclusions only to be drawn in a hypothetical manner. Moreover, the low number of events, which might be explained by the size of the cohort and length of follow-up, causes a certain chance of a bias. However, we think that results of analyses of real-world data could have an important impact on our daily treatment decisions, since these data much more accurately reflect our usual patients having certain comorbidities and inabilities. In this context, it appears fair to conclude from all our 3 analyses performed on the anagrelide registry that in a real-world population a platelet count below 600 G/L and a normal WBC count are reasonable goals in order to lower the risk of major

thrombotic events. Prospective studies on large patient cohorts are certainly needed.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

Contribution: VB collected data, performed research and wrote the manuscript. D.W, SS, EF, SH, MTK, RR and BG collected data. WS performed statistical analysis. JT wrote the manuscript. HG designed and supervised the research project, treated the patients and wrote the manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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