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Long-Term Cardiovascular Effects of Polycythemia Vera Treatment Modalities: A Systematic Review

[1] Fajar Prianto Nugroho, [2] Putri Nur Aini

[1] Faculty of Medicine, Muhammadiyah University of Yogyakarta, Special Region of Yogyakarta, Indonesia

[2] Faculty of Medicine, Lambung Mangkurat University, Banjarmasin, South Kalimantan, Indonesia

Corresponding Author : Fajar Prianto Nugroho., MD. Faculty of Medicine, Muhammadiyah University of Yogyakarta, Special Region of Yogyakarta, Indonesia. Email : fajarnugroho434@gmail.com

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ABSTRACT

Background: Polycitemia Vera (PV) is defined by the erythroid lineage's primary proliferation, which may be accompanied by hyperplasia of megakaryopoiesis and granulopoiesis. Erythropoietin (Epo) and other physiological regulators are not linked to the hyperproliferation of erythroid cells. The most common genetic abnormalities in PV are Janus-kinase 2 (JAK2) mutations. **The aim:** The aim of this study to show about long-term cardiovascular effects of polycythemia vera treatment modalities. **Methods:** By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Sciencedirect were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done. **Result:** Eight publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles. **Conclusion:** The findings imply that treating PV patients with hydroxyurea resistance or intolerance with ruxolitinib may lower the risk of arterial thrombosis.

Keyword: Polycythemia vera, treatment, cardiovascular, effecs.

INTRODUCTION

The World Health Organization (WHO) has categorized polycythemia vera (PV) as a hematological condition under myeloproliferative neoplasms (MPN). The term "MPN" is commonly used to refer to the three pathological entities that lack the Philadelphia chromosome (Ph-) but have mutations in the Janus kinase 2 (JAK2), calreticulin (CALR), or proto-oncogene, thrombopoietin receptor (MPL) genes, even though the MPN category has seven subcategories. These indicate clonal proliferations originating in stem cells and include PV, essential thrombocythemia (ET), and primary myelofibrosis (PMF). JAK2V617F, the most common JAK2 mutation linked to Ph-MPN, is located in exon 14.[1,2]

Erythrocytosis, also known as polycythemia, is the term used to describe an increase in the body's absolute amount of red blood cells (RBCs). An increase in hemoglobin levels, or hematocrit, above what is deemed physiological for the specific age and gender is the practical manifestation of this. For males, the normal RBC mass is 36 ml/kg, and for females, it is 32 ml/kg. The reference limits for normal hematocrit and hemoglobin levels differ by country, ethnicity, and altitude. For comparison, a healthy adult male's hemoglobin and hematocrit are 16 g/dL +/- 2 gm/dl and 47% +/- 6%, respectively. A menstrual adult female's hemoglobin and hematocrit are typically 13 g/dL +/- 2 gm/dl and 40% +/- 6%, respectively. A central venous hematocrit of more than 65% or a hemoglobin level more than 22 g/dL are indicators of polycythemia in neonates.[3,4]

The management of PV has been completely transformed by the new therapy options that have been discovered as a result of the detection of this mutation. PV has a wide range of clinical manifestations, from accidental detection to a full-blown case with characteristic signs and symptoms primarily related to elevated red blood cell (RBC) mass and quantity, which raises blood viscosity. Because of the defective platelet production, this increases the risk of both thrombotic and hemorrhagic consequences. Increased cytokine synthesis results in constitutional symptoms as fever, pruritus, anorexia, and weight loss. Significant morbidity and lost productivity are caused by these symptoms. Reducing thrombotic events, controlling constitutional symptoms, and stopping the

spread of cancer while minimizing the negative consequences of different treatment approaches are the cornerstones of care.[5,6]

The natural history of PV has not been impacted by current treatment in terms of overall, leukemia-free, or myelofibrosis-free survival; however, thrombosis-free survival has been positively impacted by phlebotomy, aspirin, and cytoreductive medication treatment. In the latter case, busulfan has been used safely and effectively for an even longer time, but hydroxyurea is the most widely used and scientifically proven cytoreductive drug. Ruxolutinib, a JAK1 and JAK2 inhibitor, and interferon (IFN)-α have just been added to the therapeutic arsenal, however there is no proof that they are safer over the long term or that they are better than the previous medications.[7]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast long-term cardiovascular effects of polycythemia vera treatment modalities. It is possible to accomplish this by researching of the long-term cardiovascular effects of polycythemia vera treatment modalities. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the long-term cardiovascular effects of polycythemia vera treatment modalities. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant.

Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " long-term cardiovascular effects of polycythemia vera treatment modalities." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Table 1. Search Strategy

Database	**Search Strategy**	***Hits***
Pubmed	*((*"Polycythemia*"[MeSH Subheading] OR* "Polycythemia vera*"[All Fields] OR* "Therapy*" [All Fields]) AND (*"Management*"[All Fields] OR* " Effects*"[All Fields]) AND (*"Cardiovascular*"[All Fields]) OR (*"Outcome*" [All Fields]))*	49941
Science Direct	*((*"Polycythemia*"[MeSH Subheading] OR* "Polycythemia vera*"[All Fields] OR* "Therapy*" [All Fields]) AND (*"Management*"[All Fields] OR* " Effects*"[All Fields]) AND (*"Cardiovascular*"[All Fields]) OR (*"Outcome*" [All Fields]))*	1172
Sagepub	*((*"Polycythemia*"[MeSH Subheading] OR* "Polycythemia vera*"[All Fields] OR* "Therapy*" [All Fields]) AND (*"Management*"[All Fields] OR* " Effects*"[All Fields]) AND (*"Cardiovascular*"[All Fields]) OR (*"Outcome*" [All Fields]))*	14

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.

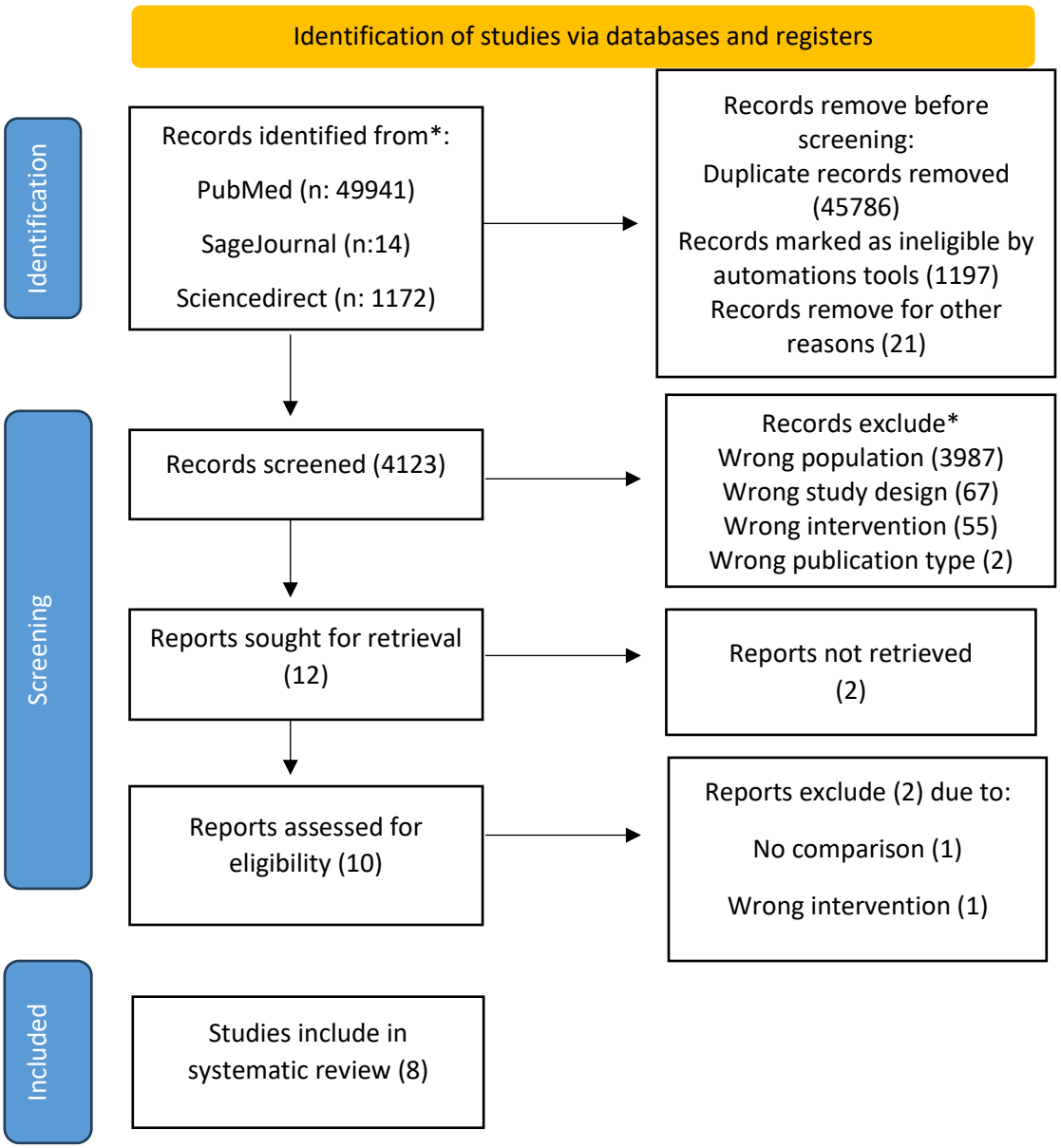

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

Table 2. Critical appraisal of Study

Parameters	(Crodel, CC et al., 2021)	(Kiladjian, JJ et al., 2020)	(Sarmento, M et al., 2023)	(Podoltsev, NA et al., 2018)	(Larran, AA et al., 2022)	(Larran, AA et al., 2017)	(Vannucchi, AM et al., 2015)	(Skov, V et al., 2022)
1. Bias related to temporal precedence Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation Was there a control group?	No	No	No	No	No	No	No	Yes
3. Bias related to confounding factors Were participants included in any comparisons similar?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care,	No	No	No	No	No	No	No	No

other than the exposure or intervention of interest?								
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 51127 publications. A thorough three-level screening strategy was used to identify only eight papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Crodel, CC et al., 2021[8]	Germany	Forty-two eligible hematologists/oncologists in private practice treating patients with MPN were recruited to participate in a paper–pencil-based survey conducted between January 2019 and March 2020 in Germany.	42	Information was gathered from the medical records of 1440 people who had been diagnosed with PV. With a median age of 72.2 years at reporting and 63.5 years at diagnosis, the patient population was older than those found in multicenter studies. With 84.7% of patients over 60 and thromboembolic problems recorded in 21.3% of patients, age was the primary factor influencing high-risk status. The percentage of participating sites that used pharmacologic cytoreduction varied greatly, ranging from 10.1 to 100%, with an average of 60.7%. Interferons were recorded for a small percentage of patients, however hydroxyurea and ruxolitinib were the most commonly utilized medications. In addition to cytoreductive treatment, a chronic need for phlebotomy was noted for 35.4% of patients. Despite the fact that the primary causes of pharmacologic cytoreduction were identified as the existence of high-risk criteria and inadequate disease

				control, 28.1% of patients had higher hematocrit values (>45%), and 38.6% of patients continued to have an elevated leukocyte count (>109/l) throughout cytoreductive treatment.
Kiladjian, JJ et al., 2019[9]	France	We report the 5-year results for a randomised, open-label, phase 3 study (RESPONSE) that enrolled patients at 109 sites across North America, South America, Europe, and the Asia-Pacific region.	342	Patient enrollment took place from October 27, 2010, to February 13, 2013, and the study ended on February 9, 2018. 222 patients out of 342 who underwent eligibility screening were randomized to receive either the best available therapy (n=112, 50%) or ruxolitinib (n=110, 50%). In the ruxolitinib group, the median time after diagnosis of polycythaemia vera was 8·2 years (IQR 3·9–12·3), while in the best available therapy group, it was 9·3 years (4·9–13·8). After 80 weeks of the study, no patient was still on the best available therapy, and 98 (88%) of the 112 patients who had been randomly assigned to the best available therapy at the beginning switched to ruxolitinib. At the time of final analysis, six of the 25 primary responders in the ruxolitinib group had made improvement. The likelihood of sustaining the primary composite response at 5 years was 74% (95% CI 51–88). 55% (95% CI 32–73) of

				patients were likely to sustain complete haematological remission, and 67% (54–77) of patients were likely to retain overall clinicohaematological responses. The chance of survival at 5 years was 91·9% (84·4–95·9) with ruxolitinib therapy and 91·0% (82·8–95·4) with the best available therapy, according to the intention-to-treat analysis that did not take crossover into account.
Sarmento, M et al., 2023[10]	Portugal	Understanding the clinical characteristics and HU treatment response of Portuguese PV patients was the goal of this multicenter, non-interventional cohort study. The modified European LeukemiaNet (ELN) criteria were used to define HU resistance/intolerance.	134	A total of 134 PV patients were included and monitored for two years, with a mean (SD) disease duration of 4.8 (5.0) years. The majority of patients were ≥60 years old (83.2%), using HU treatment (79.1%), and at high risk for thrombotic events (87.2%) at baseline. Eight hemorrhagic and ten thrombotic incidents were recorded, yielding a 17.2% 5-year likelihood of thrombo-haemorrhagic events. At the 24-month visit, the haematocrit (p = 0.007), hemoglobin (p = 0.012), and MPN10 symptom score (12.0 (11.6) vs. 10.3 (9.1); p = 0.041) all showed substantial decreases from baseline. In total, 14.4% of patients continued to be on HU during the research, and

				75.9% of patients satisfied at least one of the modified ELN criteria for HU resistance.
Podoltsev, NA et al., 2018[11]	USA	The effects of these treatments in practical settings are not well understood. We used the associated Surveillance, Epidemiology, and End Results–Medicare database to do a retrospective cohort study of older persons with PV diagnosed between 2007 and 2013.	820	The impact of phlebotomy and HU on overall survival (OS) and the incidence of thrombotic events were evaluated using multivariable Cox proportional hazards models. Out of 820 PV patients (median age = 77 years), 16.3% did not receive either phlebotomy or HU, 23.0% only received phlebotomy, 19.6% only received HU, and 41.1% received both. Thirty-seven percent (n = 305) of the patients passed away after a median follow-up of 2.83 years. Lower mortality was strongly correlated with phlebotomy (yes/no; hazard ratio [HR] = 0.65; 95% CI], 0.51-0.81; P <.01), increasing phlebotomy intensity (HR = 0.71; 95% CI, 0.65-0.79; P <.01), and a larger proportion of days covered (PDC) by HU. Both a greater HU PDC and a lower likelihood of thrombotic events were substantially correlated with phlebotomy (yes/no; HR = 0.52; 95% CI, 0.42-0.66; P <.01) and increasing phlebotomy intensity (HR = 0.46; 95% CI, 0.29-0.74; P <.01) when thrombosis

				was the outcome of interest.
Larran, AA et al., 2022[12]	Spain	The results of 377 patients with hydroxyurea resistance or intolerance from the Spanish Registry of Polycythemia Vera were retrospectively and practically analyzed based on whether they were treated with ruxolitinib (n = 105) or the best available therapy (BAT; n = 272).	377	The rate of arterial thrombosis was significantly lower in patients receiving ruxolitinib than in those on BAT (0.4% vs 2.3% annually; P =.03), and this trend continued even after controlling for the likelihood of receiving the medication (incidence rate ratio, 0.18; 95% CI, 0.02-1.3; P =.09). The incidences of severe bleeding (0.8% and 0.9%, respectively; P =.9) and venous thrombosis (0.8% and 1.1% for ruxolitinib and BAT, respectively; P =.7) did not differ significantly. Exposure to rufolitinib was not linked to an increased incidence of second primary malignancies, such as noncutaneous cancers, nonmelanoma skin cancers, or any kind of neoplasia. The two groups did not vary in terms of survival or progression to acute leukemia or myelofibrosis after a median follow-up of 3.5 years.
Larran, AA et al., 2017[13]	Spain	The aim of this study was to evaluate the need for additional phlebotomies during the	533	Hematocrit control was lower in patients who needed three or more phlebotomies annually (n=85, 16%) than in those who needed two or less (n=448, 84%). Regarding leukocyte and platelet

		first five years of hydroxyurea therapy in 533 patients with polycythemia vera.		counts, there were no appreciable variations between the two study groups. Doses of hydroxyurea were substantially greater for patients who needed three or more phlebotomies annually than for the other patients. Patients treated with hydroxyurea plus three or more phlebotomies annually had a significantly greater rate of thrombosis (20.5% vs. 5.3% after three years; P<0.0001) than those treated with hydroxyurea plus two or fewer phlebotomies annually. Thrombosis at diagnosis (HR: 4.7, 95%CI: 2.3–9.8; P<0.0001) and phlebotomy dependence (HR: 3.3, 95%CI: 1.5–6.9; P=0.002) were independent risk variables for thrombosis in multivariate analysis. The group that needed three or more phlebotomies annually had a considerably greater percentage of patients who met the European LeukemiaNet criteria of hydroxyurea resistance/intolerance (18.7% vs. 7.1%; P=0.001), primarily because of extrahematologic toxicity.
Vannucchi, AM et al., 2015[14]	UK	In a 1:1 ratio, we randomized	222	In the ruxolitinib group, 21% of patients reached the primary end point,

		phlebotomy-dependent patients with splenomegaly to either standard therapy (112 patients) or ruxolitinib (110 patients). Hematocrit control through week 32 and at least a 35% decrease in spleen volume at week 32, as determined by imaging, were the main end points.		compared to 1% in the standard-therapy group (P<0.001). Hematocrit control was attained in 60% of ruxolitinib-treated patients and 20% of patients receiving standard therapy; at least a 35% reduction in spleen volume was observed in 38% and 1% of patients in the two groups, respectively. 24% of patients in the ruxolitinib group and 9% of patients in the standard-therapy group experienced a full hematologic remission (P = 0.003); at week 32, 49% of patients had at least a 50% reduction in the total symptom score, compared to 5%. In the ruxolitinib group, 2% of patients experienced grade 3 or 4 anemia, and 5% experienced grade 3 or 4 thrombocytopenia; in the standard-therapy group, the equivalent rates were 0% and 4%, respectively. Six percent of patients in the ruxolitinib group and none in the standard-therapy group were found to have a herpes zoster infection (grade 1 or 2 in all cases). One patient receiving ruxolitinib and six individuals getting conventional therapy experienced thromboembolic events.
Skov, V et al., 2022[15]	Denmark	Nineteen patients with	123	The medicine of choice for treating individuals

		ET, 41 patients with PV, and 9 patients with PMF (data set 1), and 8 patients with ET, 21 patients with PV, and 4 patients with PMF (data set 2) as well as 21 control subjects participated in the study.		with MPNs is increasingly acknowledged to be interferon-alpha2 (rIFNα). Here, we present the first gene expression profiling study on how rIFNα affects the genes involved in oxidative stress and antioxidative defense in patients with MPNs (n = 33). It demonstrates that rIFNα upregulates downregulated antioxidative defense genes and downregulates a number of upregulated oxidative stress genes. 19 genes in ET and 29 genes in PV, including TP53 and CXCR4, were upregulated after rIFNα treatment. To sum up, the inhibition of genotoxic damage to hematopoietic cells by rIFNα may eventually reduce the likelihood of further mutations, clonal development, and the advancement of the disease towards myelofibrotic and leukemic transformation.

DISCUSSION

Despite having different morphologies, polycythemia vera (PV) and essential thrombocythemia (ET) are both chronic myeloproliferative neoplasms (MPNs) that are relatively indolent, have a lengthy survival time, and carry significant hazards of bleeding and thrombosis. According to estimates, there are 44–57 cases of PV and 38–57 cases of ET for every 100,000 people in the United States (US). Pancytosis, panmyelosis, and pleiomorphic megakaryocytes are the morphological characteristics of PV, whereas

thrombocytosis and a greater number of enlarged, mature megakaryocytes with hyperlobulated nuclei are the characteristics of ET. However, the 2016 World Health Organization (WHO) classification introduced new, lower hemoglobin and hematocrit thresholds for diagnosing PV, which could lead to some confusion between JAK2-mutated ET and PV, a disease almost exclusively driven by Janus kinase (JAK). With roughly the same percentage of patients having activating mutations/indels in JAK2, MPL (the gene encoding the thrombopoietin receptor), and calreticulin (CALR) as in primary myelofibrosis (PMF), ET has a more varied driver mutation spectrum. The remaining patients have what is known as "triple negative" disease.[16,17]

After Osler's initial reports of PV, it was rapidly recognized that minimizing excess blood was essential for patient survival. The goal value and how to maintain it have always been the problem, not the decrease in red blood cell mass. Once more, the PVSG took the first methodical approach to answering this query, ultimately establishing a goal HCT of 45%. The CYTO-PV investigation verified this value following years of ambiguity and discussion. Patients phlebotomized to an HCT below 45% and those in the range between 45% and 50% were studied in this randomized study. About 30% of the patients in the 45% or lower arm that was randomized, meanwhile, did not sustain this value. Furthermore, the goal HCTs (45% for men and 42% for women) were not suitably sex-adjusted.[18,19]

Treatment's main objectives are to lower the risk of thrombosis, lessen the severity of PV symptoms, and stop MF and/or sAML transition. For this latter goal, existing medicines are unfortunately ineffective, and blood count control may not have as much of an impact as expected. A full response was described by the European Leukemia Net (ELN) expert group as having a hematocrit of less than 45% without phlebotomy, a platelet count of less than 400 × 109/L, a leukocyte count of less than 10 × 109/L, a normal spleen size, and no symptoms associated with the disease. However, there was no correlation found between obtaining an ELN or a hematocrit response and improved mortality or fewer vascular problems in a trial of 261 PV patients who received HU and were monitored for a median of 4.4 years. There is no proof that a specific platelet or leukocyte count prevents thrombosis.[20–22]

The obvious initial measures in reducing thrombotic risk in patients with PV are to evaluate and modify these well-known cardiovascular risk factors: smoking, diabetes, high blood pressure, and cholesterol. The effectiveness and safety of low-dose aspirin were established by the findings of the European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators research. All PV patients who can tolerate it without experiencing severe bleeding or stomach adverse effects are advised to take 100 mg of aspirin per day, since this has been linked to a decreased risk of arterial and venous thromboembolic events. Phlebotomy, in particular the hematocrit objective, remained controversial due to data that indicated a proportionate rise in the rate of thrombotic events with increased hematocrit. This gap has been filled by the Cytoreductive Therapy in PV (CYTO-PV) trial, which randomly assigned participants to receive more intensive (target hematocrit, <45%) or less intensive (target hematocrit, 45%–50%) treatment. The results showed that greater hematocrit control was associated with a lower risk of major thrombosis and cardiovascular death.[23–25]

CONCLUSION

In conclusion, the findings imply that treating PV patients with hydroxyurea resistance or intolerance with ruxolitinib may lower the risk of arterial thrombosis.

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