

Case Study Series

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Cases in the Management of Polycythemia Vera: A Patient With Progressive Leukocytosis



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Case 3 of a 3-Part Series

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Patient Case

A 57-year-old man presented with complaints of headaches, dizziness, hyperhidrosis, pruritus, and early satiety (Table 1). On examination, he had mild facial and palmar plethora, with a ruddy complexion. His blood pressure was slightly elevated at 142/90 mmHg, and his spleen was palpable 2 cm below the left costal margin. A complete blood count showed a white blood cell (WBC) count of $21 \times 10^9/L$, with no peripheral blasts. The hematocrit level was also very elevated, at 66%. The platelet count was $650 \times 10^9/L$, and the erythropoietin level was undetectable. Testing using peripheral blood next-generation sequencing showed the Janus kinase 2 (*JAK2*) V617F mutation, the classic activating mutation present in 95% of cases of polycythemia vera (PV).¹⁻⁴

A bone marrow biopsy revealed several characteristics suggestive of PV. The bone marrow was hypercellular for the patient's age, and showed trilineage hematopoiesis, including erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes. This increased trilineage hematopoiesis, or excessive growth of all 3 cell lines, is also referred to as panmyelosis.

Together, these findings led to a diagnosis of PV. The patient was categorized as low risk because he was younger

than 60 years old and had no history of thrombosis. Per current guidelines from the National Comprehensive Cancer Network (NCCN) for the treatment of patients with low-risk PV, phlebotomy plus low-dose aspirin (81 mg/day) was initiated.⁵ The goal of phlebotomy was to reach and maintain a hematocrit level of less than 45%.

Phlebotomies were performed every other day, owing to the highly proliferative nature of the patient's disease. The hematocrit target of below 45% was achieved within the first month, and this level was stable for 2 months thereafter. At the 3-month follow-up, the patient reported that his headaches had diminished in severity, and he no longer experienced dizzy spells. His symptoms of early satiety and pruritus had persisted without worsening. Therefore, the disease seemed to have stabilized.

At the follow-up examination, the patient's blood pressure had improved to 118/74 mmHg. The palmar plethora was still evident. The patient's spleen remained palpable 2 cm below the left costal margin. The WBC count was $22 \times 10^9/L$, which was similar to the level at the first presentation. The patient's hematocrit level had decreased to 49%, but it still missed the target. His platelet count had increased to $774 \times 10^9/L$, which was not surprising considering that phlebotomy has minimal effect on platelets. The serum ferritin level was 9 ng/mL,

On the Cover

Colored scanning electron micrograph of a blood clot. Erythrocytes (red) are seen enmeshed in filaments of fibrin protein (white). Magnification: $\times 7000$ at 6×7 cm size.

Credit: Susumu Nishinaga / Photo Researchers, Inc.

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Table 1. Key Points of the Case

Initial Clinical Presentation	<ul style="list-style-type: none"> • A 57-year-old man presented with headaches, dizziness, hyperhidrosis, pruritus, early satiety, mild facial and palmar plethora, and a ruddy complexion • Spleen was palpable 2 cm below the left costal margin • White blood cell count, $21 \times 10^9/L$; hematocrit level, 66%; platelet count, $650 \times 10^9/L$ • <i>JAK2</i> V617F mutation
Initial Treatment	<ul style="list-style-type: none"> • Phlebotomy • Low-dose aspirin
Early Response	<ul style="list-style-type: none"> • The hematocrit target of below 45% was achieved within the first month, and this level was stable for 2 months thereafter • At the 3-month follow-up, the headaches had diminished in severity, and his dizzy spells had stopped • His symptoms of early satiety and pruritus had persisted without worsening • The disease appeared to have stabilized
Response at Follow-Up Examination	<ul style="list-style-type: none"> • The palmar plethora was still evident • The spleen remained palpable 2 cm below the left costal margin • White blood cell count, $22 \times 10^9/L$; hematocrit level, 49%; platelet count, $774 \times 10^9/L$ • Serum ferritin level, 9 ng/mL • Erythropoietin level, <3 mU/mL
Next Treatment	<ul style="list-style-type: none"> • Hydroxyurea at an initial dose of 500 mg twice daily • The dose of hydroxyurea was titrated up to 2 g/day • Continued treatment with phlebotomy and low-dose aspirin
Response Approximately 5 Months Later	<ul style="list-style-type: none"> • New symptoms of fever and severe fatigue • Pruritus worsened • The spleen was palpable 3 cm below the left costal margin • White blood cell count, $22.3 \times 10^9/L$; hematocrit level, 60%; platelet count, $780 \times 10^9/L$ • Serum ferritin level, 7 ng/mL
Next Treatment	<ul style="list-style-type: none"> • Started on ruxolitinib 10 mg twice daily
Response	<ul style="list-style-type: none"> • Required dose increases to 15 mg twice daily and then 20 mg twice daily • The patient remains on 20 mg twice daily in complete hematologic response and with full resolution of symptoms and splenomegaly

indicating iron deficiency, which is not only associated with PV but can be compounded by phlebotomy. The iron deficiency might explain the patient's increase in platelet count, in part. The erythropoietin level was less than 3 mU/mL (below the reference range).

Based on the patient's continued splenomegaly, uncontrolled levels of hematocrit, and persistently high WBC and platelet counts, cytoreductive treatment was initiated. He began treatment with hydroxyurea, the most common cytoreductive agent used in the frontline treatment of PV. The initial dose of hydroxyurea was 500 mg twice daily. This dose was titrated up to 2 g/day. The patient continued treatment with phlebotomy and low-dose aspirin.

Approximately 5 months later, the patient returned to the clinic with new symptoms, including fever and severe fatigue. His pruritus had become more severe and affected more of his body. The patient's fever could be indicative of worsening PV or intolerance to hydroxyurea. Similarly, his severe fatigue could be a symptom of PV or a side effect of hydroxyurea.

The patient's spleen had enlarged slightly and was palpable 3 cm below the costal margin. His blood pressure had normalized to 124/80 mmHg. Unfortunately, his WBC count had continued to slightly increase, to $22.3 \times 10^9/L$, and his platelet count was $780 \times 10^9/L$. Despite treatment with hydroxyurea, his hematocrit level had increased to 60%. The serum ferritin level had further decreased to 7 ng/mL, suggesting worsening iron deficiency, which was unsurprising given the continued phlebotomies.

An especially troubling finding was that the patient's hematocrit level increased to 60% despite treatment. In addition, the WBC count had not improved, and in fact had worsened, throughout treatment. The erythropoietin level remained very low, at less than 3 mU/mL (below the reference range), suggesting that the disease continued to be very active, causing overproduction of red blood cells and concomitant suppression of erythropoietin. Furthermore, the patient's platelet counts continued to rise, which could be a consequence of hyperproliferation from the PV with a component of reactive thrombocytosis

from the iron deficiency. The patient had received treatment with hydroxyurea at 2 g/day for 3 months. At this point, he met criteria for lack of efficacy (ie, resistance to hydroxyurea) per the definition from the European LeukemiaNet (Table 2).⁶ The patient might also be intolerant to hydroxyurea, as suggested by his fever, which is not a common symptom of PV.

The patient was then started on ruxolitinib at 10 mg twice daily. He eventually required dose increases to 15 mg twice daily and then to 20 mg twice daily. He remains on this dose with no phlebotomy requirement, normalization of WBC and platelet counts, and complete resolution of symptoms and splenomegaly.

Overview of PV

PV is a chronic myeloproliferative neoplasm that is characterized by an overproduction of blood cells—not only of red blood cells, which can result in blood hyperviscosity, but also of white blood cells and platelets (Table 3).⁷ Patients with PV can experience numerous significant symptoms, such as fatigue, pruritus, early satiety, abdominal discomfort, bone pain, sexual dysfunction, and excessive sweating. These symptoms can take a toll on patients, causing a significant burden and poor quality of life. Furthermore, patients with PV are at risk for thrombosis, as well as disease progression to myelofibrosis and/or transformation to acute myeloid leukemia.^{7,8}

Approximately 85% of patients with PV develop fatigue. In some patients, fatigue can be debilitating. Pruritus occurs in approximately 65% of patients with PV. Pruritus is often mild or moderate, but it can significantly impact a patient’s quality of life. Approximately one-third of patients with PV develop splenomegaly.^{9,10}

The Importance of Monitoring the WBC Count

An important goal of PV management is to achieve and maintain a hematocrit level below 45%, which is a well-documented way to improve and maintain outcomes with regard to thrombosis prevention.¹¹ Similarly, several studies have demonstrated the importance of controlling the WBC count.

ECLAP. The ECLAP study enrolled 1638 patients with PV.¹² Approximately one-third of these patients entered a multicenter, double-blind, placebo-controlled, randomized study to evaluate the safety and efficacy of low-dose aspirin (100 mg daily) as prophylactic therapy for thrombosis. The remaining patients entered a prospective, observational cohort study.

Initial reports from the study confirmed that older age (>65 years) and history of thrombosis are important risk factors for thrombotic complications.^{13,14} In the prospective study, a multivariate analysis of the baseline

Table 2. European LeukemiaNet Recommendations for the Definition of Resistance/Intolerance to Hydroxyurea in Patients With Polycythemia Vera

Definition of Resistance/Intolerance to Hydroxyurea
Need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/d of hydroxyurea OR
Uncontrolled myeloproliferation (ie, platelet count >400 × 10 ⁹ /L and WBC count >10 × 10 ⁹ /L) after 3 months of at least 2 g/d of hydroxyurea OR
Failure to reduce massive (>10 cm from the costal margin) splenomegaly by >50% as measured by palpation or failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/d of hydroxyurea OR
Absolute neutrophil count <1.0 × 10 ⁹ /L or platelet count <100 × 10 ⁹ /L or hemoglobin <10 g/dL at the lowest dose of hydroxyurea required to achieve a complete or partial clinicohematologic response ^a OR
Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematologic toxicities, such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of hydroxyurea

GI, gastrointestinal; WBC, white blood count. ^aComplete response is defined as hematocrit <45% without phlebotomy, platelet count ≤400 × 10⁹/L, WBC count ≤10 × 10⁹/L, and no disease-related symptoms. Partial response is defined as hematocrit <45% without phlebotomy or a response in 3 or more of the other criteria.

Adapted from Barbui T et al. *Leukemia*. 2018;32(5):1057-1069.⁶

WBC counts found that an elevated count was significantly associated with myocardial infarction ($P=.049$), but not with other thrombotic events.¹⁵ However, in a multivariable, time-dependent analysis, the risk of thrombosis increased in patients with a WBC count higher than 10 × 10⁹/L (Figure 1). This increase became statistically significant in patients with a WBC count higher than 15 × 10⁹/L (hazard ratio, 1.71; 95% CI, 1.10-2.65; $P=.017$). This association was stronger with arterial thrombosis events vs venous thrombosis events. These results led the study investigators to conclude that in patients with PV, an elevated WBC count of 15 × 10⁹/L or higher was an independent predictor of vascular risk.

CYTO-PV. The randomized CYTO-PV trial evaluated how well different cytoreductive therapies (phlebotomy and cytoreductive drugs) could prevent thrombotic events among patients with PV.¹¹ The patients were randomly assigned to receive treatment aimed at maintaining

Table 3. 2017 WHO Diagnostic Criteria for Polycythemia Vera

Diagnostic Criteria: Requires All 3 Major Criteria, or the First 2 Major Criteria Plus the Minor Criteria	
Major Criteria	Increased Hgb (>16.5 g/dL in men or >16.0 g/dL in women), or increased Hct (>49% in men or >48% in women), or other evidence of increased red cell volume (increased red cell mass)
	Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
	<i>JAK2</i> V617F or <i>JAK2</i> exon 12 mutation
Minor Criteria	Serum erythropoietin level below the reference range for normal

Hct, hematocrit; Hgb, hemoglobin; WHO, World Health Organization.

Adapted from Swerdlow SH et al. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2017.⁷

hematocrit levels below 45% vs treatment that aimed to maintain levels between 45% and 50%. Patients who maintained a hematocrit level below 45% had a significantly lower rate of cardiovascular death and major thrombosis. The CYTO-PV study therefore established a hematocrit level below 45% as a goal for management of PV.

During the follow-up of the CYTO-PV study, it was found that patients with high hematocrit levels also had significantly higher WBC counts as compared with patients in the low hematocrit level group ($P < .001$). However, platelet levels did not differ significantly between the arms. A multivariable time-dependent analysis was conducted to discern the effects of more stringent hematocrit control (<45%) from the lower WBC counts on thrombosis events.¹⁶ This analysis used the last WBC count recorded prior to the thrombosis event.

The study found that the risk of a thrombosis event increased as the WBC count rose.¹⁶ The hazard ratio for a major thrombosis was 1.58 (95% CI, 0.39-6.43) in patients with a WBC count of $7.0 \times 10^9/L$ to $8.4 \times 10^9/L$, 2.69 (95% CI, 0.80-9.05) in patients with a WBC count of $8.5 \times 10^9/L$ to $11.0 \times 10^9/L$, and 3.90 (95% CI, 1.24-12.3) in patients with a WBC count of $11.0 \times 10^9/L$ or higher. This association became statistically significant when the WBC count was $11.0 \times 10^9/L$ or higher ($P = .02$). Based on these results, the study investigators concluded that an elevated WBC count has a thrombogenic role in patients with PV.

REVEAL. The prospective, observational REVEAL study examined demographics, burden of disease, clinical management, patient-reported outcomes, and health care resource utilization in patients with PV.¹⁷ A total of 2510 patients with PV were enrolled into the study from 188 community and 39 academic practices across the United States.

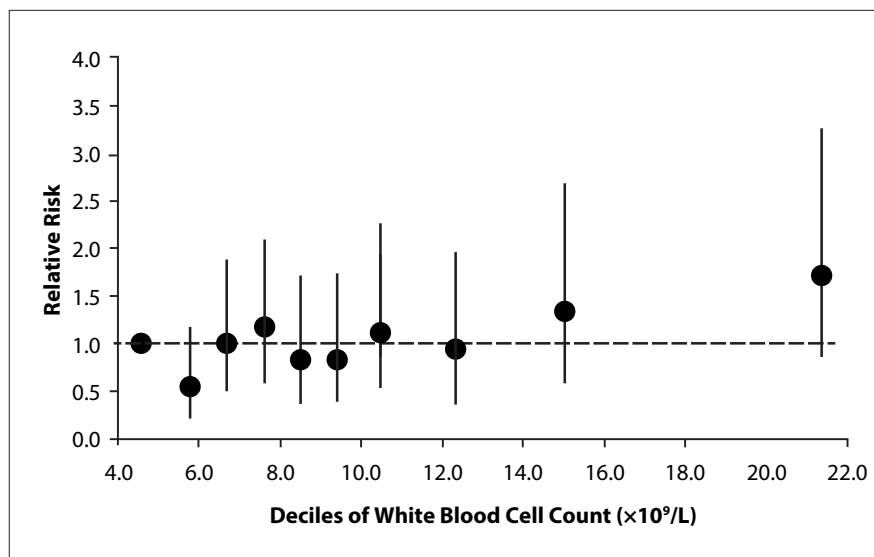
An analysis published in 2018 provided data for 1813 patients who had a complete blood count taken within 30 days of completion of the at-enrollment Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score and were evaluable.¹⁷ Items included in this questionnaire were fatigue, early satiety, abdominal discomfort, inactivity, problems with concentration, night sweats, pruritus, bone pain, fever, and weight loss. Each symptom was scored by the patient on a scale ranging from 0 (absent) to 10 (worst imaginable). The 10 individual symptom scores were then totaled.

Among the evaluable patients, hematocrit levels were below 45% in 51.5%, the WBC count was below $10 \times 10^9/L$ in 61.7%, and the platelet count was $400 \times 10^9/L$ or lower in 63.5%. Both hematocrit levels and the WBC count were controlled in 34.6%. At least 1 cell count was controlled in 89.0% of patients, at least 2 cell counts were controlled in 61.9%, and all 3 cell counts were controlled in 25.8%.

The mean total symptom score was 20.2 in patients with all 3 counts uncontrolled, 18.7 in patients who had at least 1 count controlled, 18.7 among patients who had at least 2 counts controlled, and 19.1 in patients with all 3 counts controlled. Patients with WBC control had a lower mean total symptom score compared with patients without WBC control (18.0 vs 20.2, respectively; $P = .0036$). The mean controlled WBC count was $6.83 \times 10^9/L$, whereas the mean uncontrolled WBC count was $16.33 \times 10^9/L$. Control of hematocrit levels and platelet count did not impact the mean total symptom score.

An updated analysis of the REVEAL study from 2021 provided data for 2271 patients.¹⁸ The analysis showed that elevated hematocrit levels (>45%), higher WBC counts (> $11 \times 10^9/L$), and higher platelet counts (> $400 \times 10^9/L$) were each associated with an increased risk

Figure 1. White blood cell count deciles and risk of major thrombosis among 1638 patients with polycythemia vera in an observational study by the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP). Circles indicate hazard ratios, and the bars are 95% CIs. The dotted horizontal line indicates null effect ($P > .05$). Adapted from Landolfi R et al. *Blood*. 2007;109(6):2446-52.¹⁵



of thrombotic events. Compared with alternative thresholds, a WBC count higher than $11 \times 10^9/L$ was associated with the highest risk of thrombotic events compared with a WBC count below $7 \times 10^9/L$ (hazard ratio, 2.61; 95% CI, 1.594-4.262; $P < .0001$).

An analysis of mortality in the REVEAL study showed that the estimated 4-year mortality rate exceeded 10%.¹⁹ In the 6 months before death, 31.1% of patients (59/190) had at least 1 elevated hematocrit value, 57.9% of patients (110/190) had at least 1 elevated WBC count, and 36.8% of patients (70/190) had at least 1 elevated platelet count. Uncontrolled myeloproliferation (≥ 1 elevated WBC and ≥ 1 elevated platelet count) was reported in 27.5% of patients (52/189) in the 6 months before death.

Summary

ECLAP, CYTO-PV, and REVEAL demonstrate a connection between an elevated WBC count and poor outcomes in patients with PV, including a higher risk for thrombosis as well as an increased symptom burden.^{11,12,16,17} An earlier study from 2013 identified a WBC count over $15 \times 10^9/L$ as an adverse risk factor for overall survival, as well as leukemia-free survival, in patients with PV.²⁰ The Mutation-Enhanced International Prognostic Systems for Polycythemia Vera prognostic model includes a WBC count of $15 \times 10^9/L$ or higher as an adverse prognostic feature.²¹

Preclinical studies have shown that neutrophils have a role in blood clotting. The involvement of WBCs has been traced to neutrophil extracellular trap formation, which plays a direct role in thrombogenesis. It is not yet known whether neutrophil extracellular trap formation is what ties together an elevated WBC count in patients

with PV with the associated increased risk of thrombosis. An analysis of the ECLAP study showed that a high neutrophil-to-lymphocyte ratio correlates with a higher risk of venous thrombosis among patients with PV.²² An elevated WBC count is suggestive of high inflammatory markers, which may also impact the underlying pathophysiology of thrombosis. In a mouse model, the application of the JAK1/2 inhibitor ruxolitinib impaired the formation of neutrophil extracellular traps, suggesting that JAK inhibition may effectively mitigate this impact on thrombosis.²³

Rationale for Treatment Decisions

Therapeutic Phlebotomy and Low-Dose Aspirin

Therapeutic phlebotomy and administration of low-dose aspirin (70-100 mg per day) are mainstays of upfront treatment of PV, with the main goal being prevention of thrombosis. This regimen was established in the multicenter ECLAP study, which reported a 60% reduction of combined risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, and death from cardiovascular causes with the use of low-dose aspirin. This treatment did not increase the risk of major bleeding episodes (relative risk, 1.62; 95% CI, 0.27-9.71).¹⁵

Ropeginterferon Alfa-2b

In November 2021, ropeginterferon alfa-2b, a mono-pegylated interferon administered every 2 weeks, was approved by the US Food and Drug Administration (FDA) for the treatment of PV.²⁴ The approval was based on findings from the PEGINVERA trial, which showed

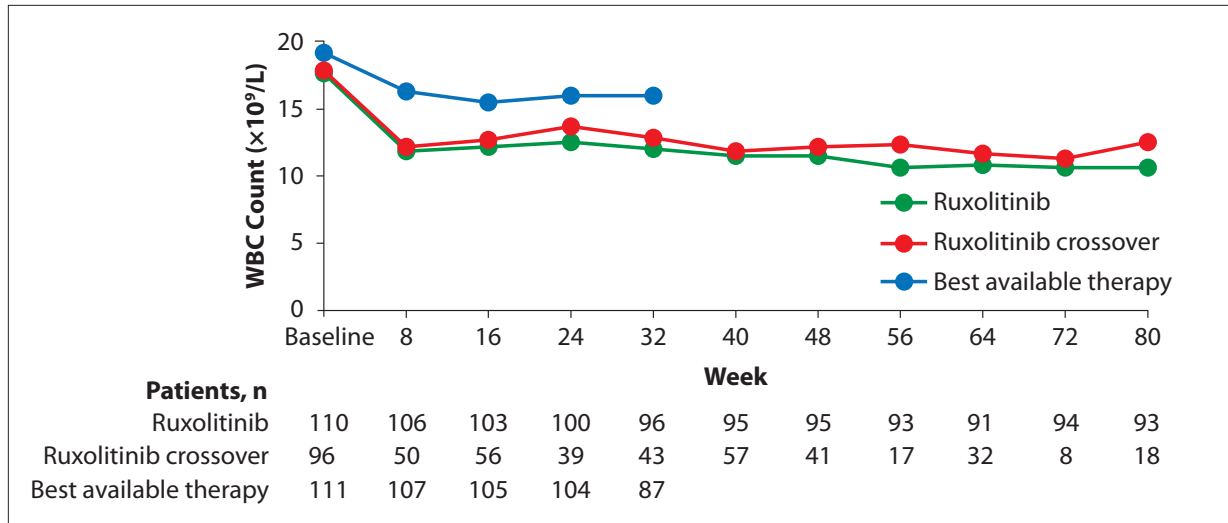


Figure 2. Mean white blood cell counts over time in an 80-week follow-up analysis of the phase 3 RESPONSE trial of ruxolitinib vs best available therapy in patients with polycythemia vera. The figure includes all data points with >5 patients. For patients in the ruxolitinib crossover group, the baseline represents the date of crossover to ruxolitinib. Data for the ruxolitinib arm and the best available therapy arm are from the 80-week data cutoff; ruxolitinib crossover data are from the 48-week data cutoff. WBC, white blood cell. Adapted from Verstovsek S et al. *Haematologica*. 2016;101(7):821-829.³⁰

that after 7.5 years of treatment, 61% of patients achieved a complete hematologic response (defined as hematocrit <45% without phlebotomy for at least 2 months since last phlebotomy, platelet counts of $\leq 400 \times 10^9/L$, WBC count of $\leq 10 \times 10^9/L$, and normal spleen size).²⁴ The most common adverse events associated with ropeginterferon alfa-2b included influenza-like illness, arthralgia, fatigue, pruritus, nasopharyngitis, and musculoskeletal pain. Ropiginterferon alfa-2b is also now included as another recommended regimen by the NCCN guidelines for the frontline treatment of low-risk PV.⁵ This recommendation is based on results of the Low-PV trial, in which the addition of ropeginterferon alfa-2b to phlebotomy and low-dose aspirin improved outcome. The response rate was 84% among patients who received ropeginterferon alfa-2b, phlebotomy, and low-dose aspirin vs 60% among those who received phlebotomy and low-dose aspirin alone (95% CI, 7-41; $P=.0075$).²⁵

Hydroxyurea

Hydroxyurea is recommended as a first-line cytoreductive treatment option for patients with PV.⁵ The addition of hydroxyurea to therapeutic phlebotomy was shown to reduce the risk of thrombosis when compared with a historical control group of patients treated with phlebotomy alone.^{26,27} Approximately one-quarter of patients will become either resistant to or intolerant of hydroxyurea. The European LeukemiaNet has provided criteria to help define and identify patients with resistance or intolerance to hydroxyurea.⁶

Ruxolitinib

In 2014, the FDA approved ruxolitinib for the treatment of PV in adults with an inadequate response to hydroxyurea or who were intolerant of hydroxyurea.²⁸ Ruxolitinib is recommended in the NCCN guidelines for the treatment of patients with PV who have become resistant or intolerant to hydroxyurea or who are poor responders to hydroxyurea.⁵ This recommendation is based on evidence from 2 trials, both of which compared ruxolitinib with best available therapy. The phase 3 RESPONSE trial enrolled phlebotomy-dependent patients with PV who were resistant or intolerant to hydroxyurea and who had splenomegaly, while the phase 3b RESPONSE-2 trial enrolled a similar population without palpable splenomegaly.²⁹⁻³³

The RESPONSE trial was an international, randomized, open-label, multicenter study of 222 adult patients with PV.²⁹ Patients were randomly assigned in a 1:1 ratio to treatment with ruxolitinib or investigator-selected best available therapy. Options for best available therapy included hydroxyurea, interferon or pegylated interferon, pipobroman, anagrelide, immunomodulators such as lenalidomide or thalidomide, or no medication. Ruxolitinib was initiated at a dose of 10 mg twice daily, with dose increases allowed to achieve and maintain a hematocrit below 45% in the absence of phlebotomy, reduce spleen size (as assessed by palpation), and normalize WBC and platelet counts.

At the primary analysis of the RESPONSE study, the composite primary endpoint of both hematocrit control

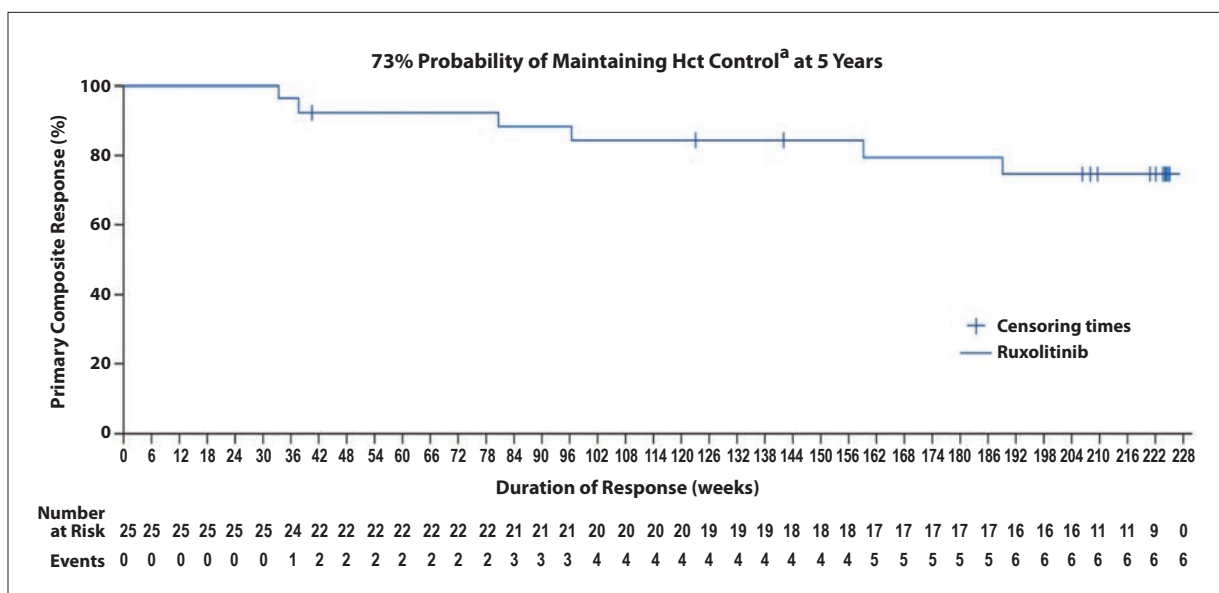


Figure 3. The median duration of primary response (patients who achieved both Hct control without phlebotomy and 35% or more reduction from baseline in spleen volume) was not reached in a 5-year analysis of the RESPONSE trial. Twenty-five patients responded. There were 6 events. Nineteen patients were censored. The crosses indicate patients who were censored. ^aAbsence of phlebotomy eligibility. Hct, hematocrit. Adapted from Kiladjian JJ et al. *Lancet Haematol.* 2020;7(3):e226-e237.³¹

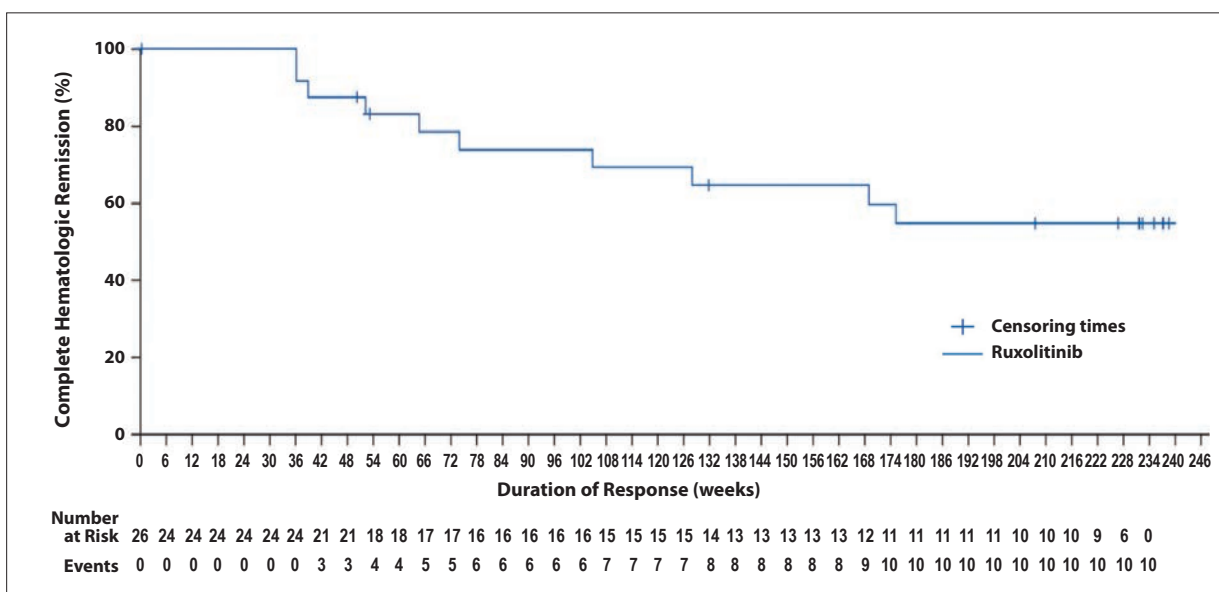


Figure 4. Complete hematologic remission in a 5-year analysis of the RESPONSE trial. Twenty-six patients responded. There were 10 events. Sixteen patients were censored. The crosses indicate patients who were censored. Adapted from Kiladjian JJ et al. *Lancet Haematol.* 2020;7(3):e226-e237.³¹

and a reduction in spleen volume of at least 35% occurred in 20.9% of the ruxolitinib arm vs 0.9% of the best-available-therapy arm ($P < .001$).²⁹ The response rates to ruxolitinib were similar in patients who had unacceptable side effects from hydroxyurea (22.0%) and in patients with an inadequate response to hydroxyurea (19.6%). A

reduction in the total symptom score of at least 50% at week 32 was reported in 49% of the ruxolitinib arm vs 5% of the standard-therapy arm.

A preplanned analysis of the RESPONSE trial occurred after all patients had completed the week 80 visit or discontinued treatment.³⁰ At week 32, the primary

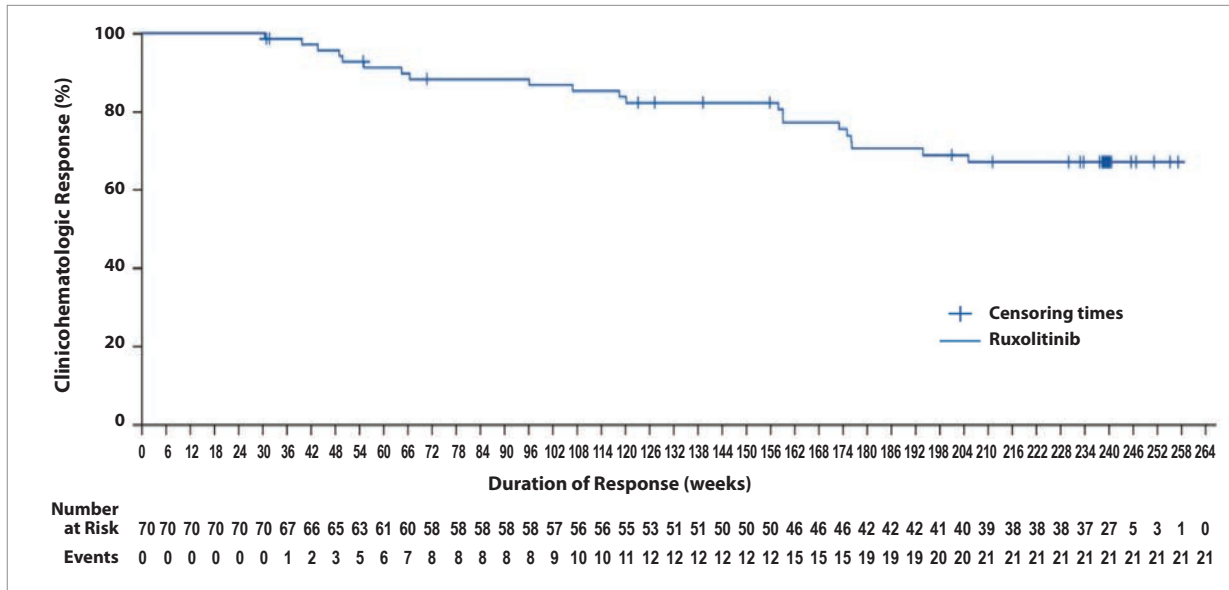


Figure 5. Overall clinicohematologic response among patients treated with ruxolitinib in a 5-year analysis of the RESPONSE trial. Seventy patients responded. There were 21 events. Forty-nine patients were censored. The crosses indicate patients who were censored. Adapted from Kiladjian JJ et al. *Lancet Haematol.* 2020;7(3):e226-e237.³¹

response was achieved by 22.7% of patients randomly assigned to ruxolitinib vs 0.9% of patients randomly assigned to best available therapy. Hematocrit control was reported in 60.0% vs 18.8%, and a spleen response was found in 40.0% vs 0.9%. Among the patients originally randomly assigned to the ruxolitinib arm, mean WBC counts decreased from $12.0 \times 10^9/L$ to $10.7 \times 10^9/L$ between weeks 32 and 80 (Figure 2).

In a 5-year follow-up of the RESPONSE study, ruxolitinib continued to improve the primary endpoint.³¹ A total of 74% (95% CI, 51-88) of patients treated with ruxolitinib maintained a primary response at 224 weeks (starting from week 32). The median duration of primary response to ruxolitinib had not been reached at the time of study completion (Figure 3). The probability of complete hematologic remission at 5 years was 55% (95% CI, 32-73; Figure 4). Among the 26 patients who had achieved a complete hematologic remission at week 32, 10 (38%) had progressed by week 256. Overall, fewer phlebotomies were required in patients who were either initially randomly assigned to ruxolitinib or had crossed over to ruxolitinib vs in patients treated with best available therapy. At week 32, 70 patients had an overall clinicohematologic response. Among these patients, 30% had progressed by week 256. The probability of maintaining a clinicohematologic response at 224 weeks was 67% (95% CI, 54-77; starting from week 32; Figure 5). The median duration of a clinicohematologic response was not reached.

Safety outcomes reported at the primary analysis demonstrated that both ruxolitinib and best available therapy were associated with low rates of grade 3 or 4 nonhematologic adverse events.²⁹ Herpes zoster infections (grade 1/2) occurred in 6.4% of ruxolitinib-treated patients compared with no patients receiving best available therapy. At the 5-year follow-up, the rates of non-hematologic adverse events were lower with ruxolitinib vs best available therapy.³¹ The most common of these events reported with ruxolitinib vs best available therapy were pruritus (7.0 per 100 patient-years of exposure vs 6.1 per 100 patient-years of exposure, respectively), diarrhea (7.0 vs 3.6), increased weight (6.1 vs 4.2), headache (5.8 vs 5.2), arthralgia (5.6 vs 3.3), fatigue (5.1 vs 3.9), and muscle spasms (5.1 vs 3.3).

The phase 3b RESPONSE-2 trial followed a similar design to RESPONSE, but the patients did not have splenomegaly.³² In the primary analysis, hematocrit control was reported in 62% of patients randomly assigned to ruxolitinib vs 19% of those randomly assigned to best available therapy (odds ratio, 7.28; 95% CI, 3.43-15.45; $P < .0001$).

A 5-year analysis of the RESPONSE-2 study was published in May 2022.³³ The median follow-up was 67 months (interquartile range, 65-70). The trial permitted patients in the control arm to cross over to the ruxolitinib arm, and 77% of patients did so between weeks 28 and 80. No patients received best available therapy after week 80, per protocol.

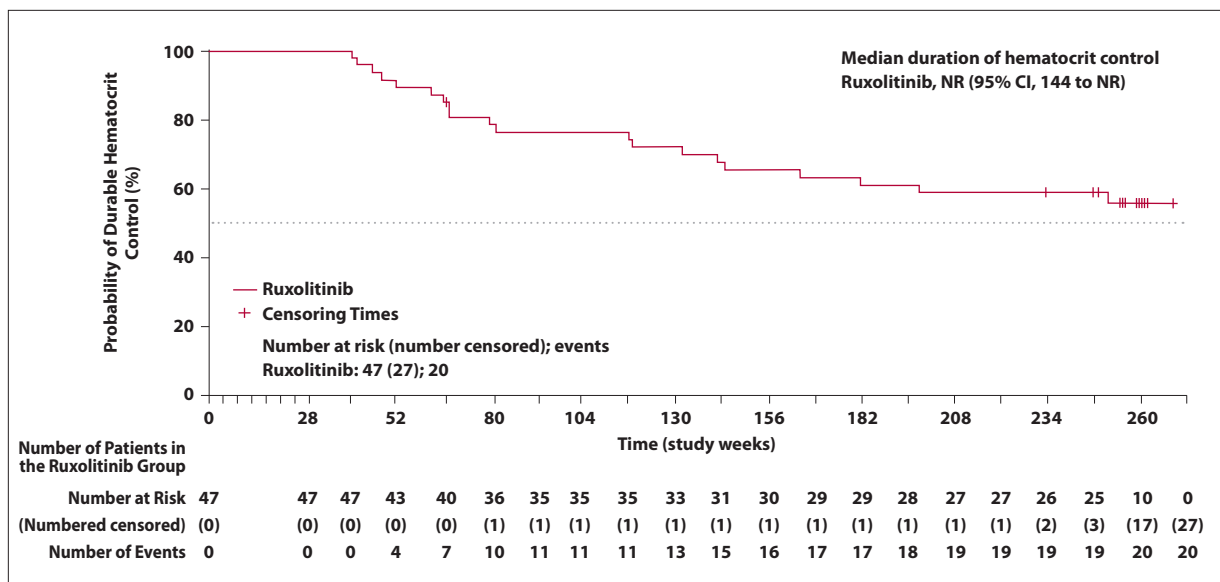


Figure 6. The median duration of hematocrit control was not reached in a 5-year analysis of patients treated with ruxolitinib in the phase 3b RESPONSE-2 trial. NR, not reached. Adapted from Passamonti F et al. *Lancet Haematol.* 2022;9(7):e480-e492.³³

Durable hematocrit control at week 260 was reported in 22% (95% CI, 13-33) of patients in the ruxolitinib arm.³³ The estimated median duration of hematocrit control was not reached among patients receiving ruxolitinib (95% CI, 144 to not reached; Figure 6). Fewer phlebotomies were needed among patients treated with ruxolitinib. In the ruxolitinib arm, the median level of hematocrit was maintained below 45%. The 5-year rates of overall survival were 96% (95% CI, 87-99) with ruxolitinib vs 91% (95% CI, 80-96) with best available therapy.

The exposure-adjusted rates of any-grade thromboembolic events were 1.5% per 100 person-years with ruxolitinib vs 3.7% per 100 person-years with best available therapy.³³ In the ruxolitinib arm, hypertension was the most frequently reported grade 3/4 adverse event (exposure-adjusted per 100 patient-years), occurring in 2.4% of patients (vs 5.6% in the control arm).

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