JKMS

Original Article
Oncology & Hematology

Check for updates

Address for Correspondence:
Sung-Yong Kim, MD, PhD
Division of Hematology, Department of
Internal Medicine, Konkuk University Medical
Center, Konkuk University, 120-1 Neungdong-
ro, Gwangjin-gu, Seoul 05030, Korea.
Email: sykim@kuh.ac.kr

ORCID iDs
Sung-Eun Lee
https://orcid.org/0000-0002-9810-2050
Junshik Hong
https://orcid.org/0000-0002-7829-397X
Soo-Mee Bang
https://orcid.org/0000-0002-0938-3007
Jinny Park
https://orcid.org/0009-0005-3186-3591
Chul Won Choi
https://orcid.org/0000-0002-3032-4239
Sung Hwa Bae
https://orcid.org/0000-0002-5279-6341
Min Kyoung Kim
https://orcid.org/0000-0003-0088-0995
Seug Yun Yoon
https://orcid.org/0000-0001-8228-0218
Sung-Yong Kim
https://orcid.org/0000-0002-3697-1314

Differences in Clinical Outcomes Between Hydroxyurea-Resistant and -Intolerant Polycythemia Vera Patients

Sung-Eun Lee [iD],[1] Junshik Hong [iD],[2] Soo-Mee Bang [iD],[3] Jinny Park [iD],[4]
Chul Won Choi [iD],[5] Sung Hwa Bae [iD],[6] Min Kyoung Kim [iD],[7] Seug Yun Yoon [iD],[8] and
Sung-Yong Kim [iD] [9]

[1]Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of
Korea, Seoul, Korea
[2]Divison of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University
Hospital, Seoul, Korea
[3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University
College of Medicine, Seongnam, Korea
[4]Divison of Hematology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon,
Korea
[5]Divison of Hematology-Oncology, Department of Internal Medicine, Korea University Guro Hospital, Seoul,
Korea
[6]Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, Korea
[7]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea
[8]Division of Hematology-Oncology, Department of Internal Medicine, Soonchunhyang University College of
Medicine, Seoul, Korea
[9]Divison of Hematology, Department of Internal Medicine, Konkuk University Medical Center, Konkuk
University, Seoul, Korea

ABSTRACT

Background: Previous studies have suggested that patients with polycythemia vera (PV)
who exhibit hydroxyurea-resistance (HU-R) and -intolerance (HU-I) may have distinct
characteristics and clinical outcomes. However, to date, no studies have reported a
comparison between these two groups or assessed prognostic factors in these patients.
Methods: The objective of this study was to evaluate clinical outcomes and identify
prognostic factors among PV patients with HU-R or HU-I. We conducted a review of PV
patients who received frontline treatment with HU from nine centers and identified 90
patients with HU-R or HU-I.
Results: The cumulative incidence of thrombosis after 7 years of HU-R/I was 21.4%, and
the incidence of disease progression was 22.5%. Comparing the HU-R and HU-I groups,
the HU-R group had a significantly higher rate of disease progression (36.7% vs. 0.56%, P =
0.009), while there was no significant difference in thrombosis incidence (19.0% vs. 22.9%,
P = 0.463). Multivariate analysis revealed that HU-R was an independent prognostic factor for
progression-free survival (hazard ratio, 6.27, 95% confidence interval, 1.83–21.47, P = 0.003).
Additionally, higher lactate dehydrogenase levels, multiple cardiovascular risk factors, and
prior thrombosis were identified as unfavorable predictors of overall survival.
Conclusion: These findings suggest that patients with HU-R face a higher risk of
hematological transformation, but have a comparable risk of thrombosis to patients with HU
intolerance. These distinctions should guide decisions on second-line treatment options and
clinical trials involving these patients.

Keywords: Polycythemia Vera; Hydroxyurea; Drug Resistance; Intolerance

Author Contributions

Conceptualization: Kim SY. Data curation: Lee SE. Formal analysis: Kim SY, Lee SE. Methodology: Hong J, Bang SM. Validation: Yoon SY. Writing - original draft: Lee SE. Writing - review & editing: Kim SY, Park J, Choi CW, Bae SH, Kim MK.

INTRODUCTION

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by clonal myeloid stem cell proliferation driven by somatic driver mutations in Janus kinase-2 (JAK-2).[1-3] It exhibits a distinct natural history marked by a high incidence of thrombosis and a propensity to transform into more advanced myeloid malignancies, such as post-PV myelofibrosis, myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML).[4-7] The current therapeutic approach for PV primarily aims to reduce the risk of thrombotic events through the use of phlebotomy and cytoreductive agents due to limited options for altering the disease's natural course.[8] While phlebotomy and low-dose aspirin are considered the initial standard of care, cytoreduction using therapeutic drugs is recommended for high-risk and symptomatic low-risk patients.[9] Hydroxyurea (HU) is commonly employed as a first-line cytoreductive agent due to its effective activity in reducing cell proliferation and generally acceptable safety profile.[9-11]

However, previous retrospective studies have demonstrated that 5–11% of PV patients experience resistance to HU (HU-R), while approximately 5–13% of patients are intolerant to HU (HU-I) due to undesirable side effects.[11-14] Inadequate control of blood counts resulting from various factors, including HU-R or HU-I, is associated with unfavorable clinical outcomes.[15] Nevertheless, there is limited data available on the prognostic factors among these patients who develop HU-R or HU-I. Direct comparisons between patients with HU-R and HU-I have not been conducted, and prognostic factors related to clinical outcomes, such as thrombosis, bleeding, disease progression, and survival, remain unclear for patients experiencing HU-R or HU-I.[13] Currently, the therapeutic options for both groups of patients do not differ, and most clinical trials investigating second-line therapies have enrolled patients with HU-R or HU-I without considering potential clinical distinctions between the two groups.[9] This study aims to compare the clinical outcomes of these two groups and identify prognostic factors to facilitate clinical decision-making and patient monitoring.

METHODS

Study patients

Among patients diagnosed with PV according to the World Health Organization classification in nine centers of the MPN working party of the Korean Society of Hematology, patients who received cytoreductive therapy with HU and met HU-R/I criteria as defined by the European LeukemiaNet (ELN) were enrolled in this study.[16] The study patients with HU-R/I were identified through medical records from the period 2013–2022. The main clinical and laboratory data at the time of PV diagnosis and the development of HU-R/I, including age, sex, cardiovascular risk factors (diabetes, hypertension, smoking, and hyperlipidemia), history of thrombosis, hemoglobin level, leukocyte count, platelet count, serum erythropoietin level, and JAK-2 mutation, were collected for all patients. Lactate dehydrogenase (LDH) levels were collected and calculated as the fold increase above the upper limit of normal. Information on second-line treatment was also collected. Thrombosis and bleeding occurrences, progression to more advanced hematologic malignancy, and causes of death were assessed.

Definitions

Thrombosis was defined according to the International Classification of Diseases, 9th revision. Minor occlusive events, such as erythromelalgia and superficial thrombophlebitis of the extremities, were not considered thrombosis events. Major bleeding was defined as symptomatic bleeding in a critical organ or overt bleeding causing a decrease in the hemoglobin level of more than 2.0 g/dL.[17] Response to HU was categorized using ELN criteria.[16,18] HU-R and HU-I were defined as fulfilling at least one of the criteria. Among the five criteria, need for phlebotomy, uncontrolled myeloproliferation, and failure to reduce spleen size were defined as "HU-R," while leg ulcer and other hydroxyurea-related toxicity were defined as "HU-I." In our present study, cytopenia at the lowest dose of HU required to achieve a complete response was defined as HU-R.

Statistical analyses

We evaluated the characteristics and outcomes of HU-R/I patients, including the cumulative incidence of progression to myelofibrosis, MDS, or AML, the cumulative incidence of thrombosis, and survival. Prognostic factors were identified for thrombosis-free survival (TFS), progression-free survival (PFS), and overall survival (OS) after HU-R/I occurrence in the study patients.

The characteristics of the patients who had HU-R and HU-I were compared using the χ^2 test or the Mann-Whitney U test. Progression and thrombosis curves were plotted according to cumulative incidence estimates and compared with the Gray test. The TFS, PFS, and OS probabilities were calculated using Kaplan-Meier estimates and compared between the two groups using the log-rank test. Survival analyses and time-to-event curves were calculated from the date of HU-R/I occurrence. Multivariate analysis with Cox's proportional hazard regression was used to define the prognostic factors for thrombosis, progression, TFS, PFS, and OS using the backward method. The variables included in the multivariate analysis were study group (HU-R vs. HU-I), age (≥ 65 vs. < 65 years), gender (male vs. female), LDH level (higher vs. lower), number of cardiovascular risk factors (≥ 2 vs. < 2), and prior thrombosis (yes vs. no). Continuous variables were categorized into dichotomous variables using a median split when multivariate analysis was conducted. P values were determined by two-sided tests, and P values of < 0.05 were considered statistically significant. Analyses were performed using the Statistical Package for the Social Sciences, version 28.0 (SPSS 28.0; IBM Corp., Chicago, IL, USA).

Ethics statement

This study was designed by the MPN working party of the Korean Society of Hematology, approved by the Institutional Review Board of Konkuk University Medical Center (KUH 2022-05-058), and conducted in accordance with the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study.

RESULTS

Patients and treatment

A total of 90 patients with HU-R/I were enrolled in this study. Among them, 44 and 46 patients fulfilled the ELN criteria defining HU-R or HU-I, respectively. The main clinical and hematological characteristics of the patients at the time of developing HU-R/I are listed in **Table 1**. A maximal HU dose of 1,350 ± 551 mg/day was used to try to maintain hematocrit

Table 1. Patient characteristics at the time of development of resistance or intolerance

Variables	All (N = 90)	HU-R (n = 44)	HU-I (n = 46)	P
Age, yr	67 ± 12	71 ± 12	63 ± 10	0.001
Male	47 (52.2)	21 (47.7)	26 (56.5)	0.404
Time from HU treatment to HU-R/I, yr	4.9 ± 4.5	5.8 ± 5.3	4.0 ± 3.4	0.055
LDH, fold × UNL	1.66 ± 0.97	2.44 ± 1.33	1.92 ± 0.66	0.050
JAK-2 mutation[a]	87/89 (97.8)	42/43 (97.7)	45/46 (97.8)	1.000
HU maximal dosage, mg/d	1,350 ± 551	1,414 ± 633	1,288 ± 459	0.282
History of prior thrombosis	19 (21.1)	14 (31.8)	5 (10.9)	0.020
Cardiovascular risk factors				
Diabetes mellitus	16	5	11	0.169
Hypertension	49	24	25	1.000
Smoking	13	7	6	0.770
Dyslipidemia	15	6	9	0.575

Values are presented as mean ± standard deviation or number (%).
HU-R = hydroxyurea-resistance, HU-I = hydroxyurea-intolerance, HU = hydroxyurea, LDH = lactate dehydrogenase, UNL = upper normal level, JAK-2 = Janus kinase-2.
[a]One patient in HU-R group was not tested for JAK-2 mutation.

levels below 45% without significant intolerance. Of the 90 patients, 83 (92.2%) received low-dose aspirin during treatment with HU.

Among the 44 patients in the HU-R group, at least one of the criteria defining resistance developed 5.8 ± 5.3 years after HU treatment. Seven patients developed uncontrolled myeloproliferation despite having received 2 g/day of HU for more than three months. Thirty-seven patients developed neutropenia (absolute neutrophil count < 1 × 10^9/L), anemia (haemoglobin < 10.0 g/dL), or thrombocytopenia (platelet count < 100 × 10^9/L) at the lowest dose of HU required to achieve a hematologic complete response.

Forty-six patients in the HU-I group met the criteria of HU-I 4.0 ± 3.4 years after HU treatment. Seven patients developed leg ulcers at a median HU dose of 1,000 mg/day (range 750–1,500). Other unacceptable mucocutaneous manifestations occurred in 20 patients at various HU doses ranging from 250 mg to 2,000 mg/day (median, 1,125 mg/day). Nine patients had intolerant gastrointestinal symptoms, and four patients developed other intolerant side effects related to HU.

Patients with HU-R were older at the time of diagnosis of PV (66.7 ± 13.2 years, vs. 59.8 ± 11.2 years in the HU-I group, $P = 0.016$), had longer times to developing HU-R/I, and thus, were older at the time of HU-R/I development compared with those with HU-I (**Table 1**). There was a trend toward a lower HU maximal dosage taken in the HU-I group compared to the HU-R group. The majority of the study patients continued HU treatment with dose modification or intermittent discontinuation with anagrelide added to control platelet counts until disease progression or death because of limited second-line treatment options during the observed period. HU was changed to either interferon or ruxolitinib in 11 of 90 study patients. There was no difference in the proportion of patients receiving non-HU second-line treatment between the two groups ($P = 0.316$).

Risk of thrombosis and disease progression

After HU-R/I development, seven (7.8%) of the study patients experienced thrombotic events (**Table 2**), including cerebral infarction (n = 3), mesenteric infarction (n = 1), myocardial infarction (n = 2), and peripheral arterial thromboembolism (n = 1). The type of thrombosis did not differ between the two groups ($P = 0.628$). The cumulative incidence of thrombosis

Table 2. Outcomes after development of HU-R or HU-I in study patients

Variables	All (N = 90)	HU-R (n = 44)	HU-I (n = 46)	P
F/U duration from HU-R/I, yr	3.2 ± 3.1	3.6 ± 3.6	2.9 ± 2.5	0.302
Thrombosis	7 (7.8)	5 (11.4)	2 (2.4)	0.261
Cumulative incidence of thrombosis, at 7 yr	21.4 ± 8.6%	19.0 ± 10.0%	22.9 ± 14.4%	0.463
Progression	14 (15.6)	12 (24.0)	2 (4.9)	0.003
Myelofibrosis	7	6	1	
MDS	4	4	0	
MF, MDS, and AML[a]	1	1	0	
MF and AML[b]	1	0	1	
AML	1	1	0	
Cumulative incidence of progression, at 7 yr	22.5 ± 6.5%	36.7 ± 10.1%	0.56 ± 3.9%	0.009
Mortality at 7 yr	37.9 ± 9.6%	42.5 ± 10.6%	32.3 ± 17.8%	0.060
Cause of death (n = 14)				0.413
Infection	8	5	3	
Thrombosis or bleeding	2	2	0	
AML	2	2	0	
Breast cancer	1	1	0	
Unknown	1	1	0	

HU-R = hydroxyurea-resistance, HU-I = hydroxyurea-intolerance, F/U = follow-up, MF = post-polycythemia vera myelofibrosis, MDS = myelodysplastic syndrome, AML = acute myeloid leukemia.
[a]One patient in the HU-R group progressed to MF, MDS, and AML sequentially.
[b]One patient in the HU-I group progressed to MF and AML sequentially.

seven years after HU-R/I was estimated at 19.0% in the HU-R group and 22.9% in the HU-I group (*P* = 0.463; **Fig. 1A**).

Fourteen patients had disease progression after HU-R/I development. Five patients developed either MDS (n = 4) or AML (n = 1) without experiencing myelofibrosis. Nine (9.9%) patients developed myelofibrosis, of whom one patient group progressed to MDS and another progressed to MDS and AML sequentially. The period of time from HU-R/I development to disease progression was 11.1 months (range 0.12–193.5). The cumulative incidence of progression at seven years after HU-R/I occurrence was 22.5%. The HU-R group showed
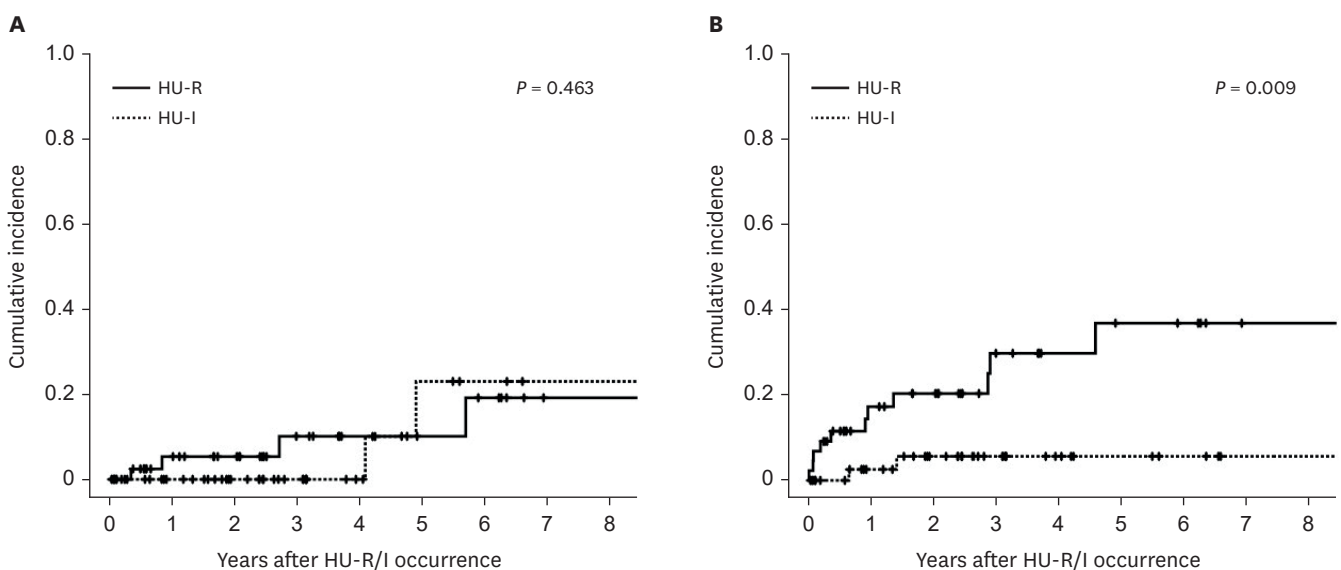

Fig. 1. Cumulative incidence of thrombosis (**A**) and disease progression (**B**) of polycythemia vera patients after developing HU-R or HU-I.
HU-R = hydroxyurea-resistance, HU-I = hydroxyurea-intolerance.

a higher cumulative incidence of progression at seven years compared to the HU-I group (36.7% vs. 0.56% in the HU-I group, P = 0.009; **Fig. 1B**).

Survival rates and causes of death

The seven-year probability of TFS, PFS, and OS for the study patients was 56.6 ± 9.2%, 51.8 ± 9.4%, and 62.1 ± 9.6%, respectively. The patients in the HU-R group had significantly lower PFS (40.2% vs. 66.1% in the HU-I group, P < 0.001; **Fig. 2A**). They also showed a trend toward lower TFS (51.0% vs. 62.1% in the HU-I group; P = 0.055) and lower OS (57.5% vs. 67.7% in the HU-I group; P = 0.060; **Fig. 2B**) compared to patients with HU-I.

Fourteen patients died during the observation period (**Table 2**). In the HU-R group, two patients died of AML, and the others died of infections (n = 5), vascular complications (n = 2), breast cancer (n = 1), and an unknown cause (n = 1). In the HU-I group, all three patients died of infection. The mortality at seven years was 42.5% in the HU-R group and 32.3% in the HU-I group (P = 0.06).

Predictors of thrombosis, progression, and survival

Univariate and multivariate analyses were performed to identify independent risk factors for disease progression and thrombosis after the development of HU-R/I (**Table 3**). HU-R was identified as an independent risk factor for disease progression (hazard ratio [HR], 5.57, 95% confidence interval [CI], 1.22–25.54, P = 0.027), while the analyses did not identify any risk factors for thrombosis.

Regarding survival, HU-R remained an independent risk factor for PFS after adjusting for other potential confounding factors (HR, 6.27, 95% CI, 1.83–21.47, P = 0.003; **Table 4**). The independent predictors for unfavorable OS were prior thrombosis (HR, 5.50, 95% CI, 1.56–19.45, P = 0.008), higher LDH levels (HR, 6.56, 95% CI, 1.53–28.04, P = 0.011), and more than one cardiovascular risk factor (HR, 4.03, 95% CI, 1.10–14.73, P = 0.035). Neither univariate nor multivariate analysis identified any predictors of TFS.
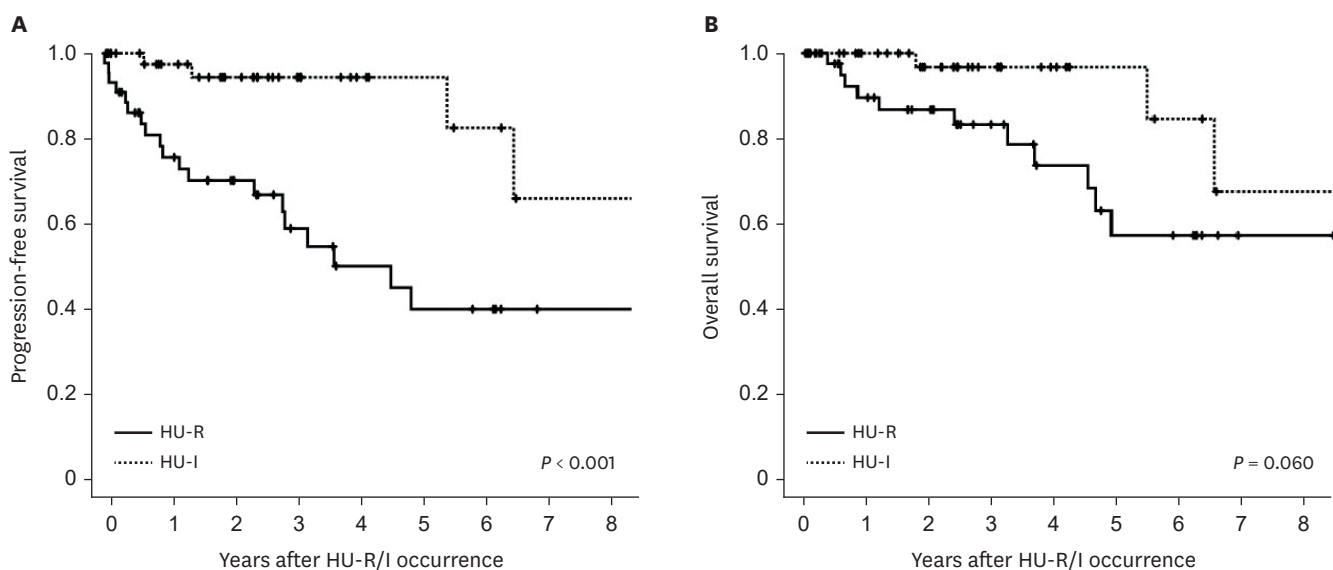

Fig. 2. Progression-free survival (**A**) and overall survival (**B**) of polycythemia vera patients after developing HU-R or HU-I.
HU-R = hydroxyurea-resistance, HU-I = hydroxyurea-intolerance.

Table 3. Risk factors for thrombosis and disease progression after development of HU-R or HU-I

Variables	Incidence of disease progression				Incidence of thrombosis			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age ≥ 65 yr (vs. < 65 yr)	1.33 (0.44–4.09)	0.615		NS	5.27 (0.61–45.50)	0.131		NS
Male (vs. female)	0.91 (0.30–2.73)	0.866		NS	1.72 (0.38–7.80)	0.480		NS
LDH, higher[a] (vs. lower)	1.15 (0.36–3.67)	0.817		NS	0.39 (0.04–3.88)	0.423		NS
Cardiovascular risk factors[b] ≥ 2 (vs. < 2)	1.42 (0.46–4.36)	0.537		NS	2.61 (0.52–13.11)	0.244		NS
Prior thrombosis	4.96 (1.66–14.78)	0.004		NS	1.34 (0.24–7.37)	0.737		NS
Lead time to HU-R/I, longer[c] (vs. shorter)	2.239 (0.727–6.896)	0.153		NS	2.275 (0.502–10.304)	0.286		NS
HU-R (vs. HU-I)	4.76 (1.09–20.85)	0.038	5.57 (1.22–25.54)	0.027	2.33 (0.425–12.76)	0.330		NS

HR = hazard ratio, CI = confidence interval, LDH = lactate dehydrogenase, HU-R = hydroxyurea-resistance, HU-I = hydroxyurea-intolerance, NS = not significant.
[a]"Higher" means more than 1.32-fold of upper normal limit (median value of all study patients).
[b]Cardiovascular risk factors: diabetes, smoking, dyslipidemia, and hypertension.
[c]Longer lead time is defined as more than 3.9 years from diagnosis of polycythemia vera to development of HU-R/I (median value of all study patients).

Table 4. Prognostic factors for progression-free survival and overall survival

Variables	Progression-free survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age ≥ 65 yr (vs. < 65 yr)	2.40 (0.94–6.10)	0.066		NS	5.10 (1.14–22.83)	0.033		NS
Male (vs. female)	1.11 (0.48–2.54)	0.812		NS	1.82 (0.62–5.30)	0.276		NS
LDH, higher[a] (vs. lower)	1.63 (0.64–4.15)	0.304		NS	2.36 (0.68–8.20)	0.175	6.56 (1.53–28.04)	0.011
Cardiovascular risk factors[b] ≥ 2 (vs. < 2)	2.0 (0.93–4.67)	0.086		NS	4.07 (1.35–12.21)	0.012	4.03 (1.10–14.73)	0.035
Prior thrombosis	4.11 (1.81–9.36)	0.001		NS	3.27 (1.14–9.37)	0.027	5.50 (1.56–19.45)	0.008
Lead time to HU-R/I, longer[c] (vs. shorter)	1.907 (0.832–4.368)	0.125		NS	1.993 (0.686–5.792)	0.196		NS
HU-R (vs. HU-I)	5.12 (1.74–15.05)	0.003	6.27 (1.83–21.47)	0.003	3.21 (0.89–11.55)	0.074		NS

HR = hazard ratio, CI = confidence interval, LDH = lactate dehydrogenase, HU-R = hydroxyurea-resistance, HU-I = hydroxyurea-intolerance, NS = not significant.
[a]"Higher" means more than 1.32-fold of upper normal limit (median value of all study patients).
[b]Cardiovascular risk factors: diabetes, smoking, dyslipidemia, and hypertension.
[c]Longer lead time is defined as more than 3.9 years from diagnosis of polycythemia vera to development of HU-R/I (median value of all study patients).

DISCUSSION

The survival of PV patients with HU-R/I was unfavorable. The probability of OS was 62.1% seven years after the development of HU-R or HU-I. Almost all participants in the study had to continue HU treatment with dose adjustments or intermittent discontinuation even after developing HU-R or HU-I. This was due to limited second-line treatment options for HU-R/I patients in Korea, as ruxolitinib and interferon use were restricted by the National Public Health Insurance Service. Therefore, our data provide insights into the clinical course of PV patients with HU-R/I who did not receive second-line therapeutic agents. Previous studies have shown that inadequate control of hematocrit and leukocyte counts increases the risk of thrombosis and mortality, which may partially explain the unfavorable survival outcomes observed in our study patients.[12,19]

Importantly, patients with HU-R had a higher risk of disease progression and lower PFS compared to patients with HU-I. However, the risk of thrombosis and time to first thrombotic event were similar between the two groups. Previous research suggested that HU-R in PV patients was associated with the acquisition of non-driver genetic mutations, implying a higher likelihood of disease progression compared to patients with HU-I.[20] The risk of thrombosis was linked to suboptimal control of blood counts; hence, there was no significant difference in thrombosis risk between the patient groups. In our study cohort, a limited subset of patients received ruxolitinib and interferon as their second-line therapeutic interventions. To mitigate potential confounding effects stemming from interferon and ruxolitinib treatment when comparing the HU-R and HU-I groups, we conducted a parallel

analysis exclusively on patients who did not undergo interferon or ruxolitinib treatment. Remarkably, this secondary analysis yielded congruent results to those obtained when analyzing the entire study population. Furthermore, a minority of patients were excluded from aspirin treatment based on the discretion of their attending physicians. To ensure consistency, we confined our analysis solely to patients who were administered aspirin, and this sub-analysis also exhibited concordant results with our primary findings.

No statistical difference in OS was seen between the two groups despite the difference in progression risk because both HU-R and HU-I patients had similar major causes of death, primarily infections. Although the difference in OS between the two groups did not differ significantly, there was a trend toward lower OS in HU-R patients (HR, 3.21, 95% CI, 0.89–11.55, $P = 0.074$). The fact that infections, thrombosis, and disease progression were the main causes of death in our study population suggests that various factors can influence the survival of HU-R/I patients. Multivariate analysis revealed that high LDH levels, more than one cardiovascular risk factor, and prior thrombosis were predictors of unfavorable OS. Our study identified higher LDH levels at the time of HU-R or intolerance development as a prognostic factor for poorer OS. This finding aligns with previous research suggesting that LDH levels at the time of PV diagnosis could serve as a prognostic biomarker.[21] The relationship between elevated LDH levels and patient survival has not been fully elucidated. Elevated LDH levels are associated with infection, organ damage caused by thrombosis, and more advanced or aggressive disease. In our study, causes of death included infections, thrombosis, and AML, which partially explains why higher LDH levels were associated with lower OS in our patient cohort.

We compared the characteristics of patients with HU-R and HU-I at the time of developing HU-R/I. Patients with HU-R were older at the time of PV diagnosis compared to patients with HU-I ($P = 0.016$), indicating a higher prevalence of resistance among older patients. Furthermore, the development of resistance appeared to require a longer period of time compared to the development of intolerance ($P = 0.055$). Previous studies have suggested that longer disease duration and older age in PV patients are associated with a higher risk of disease progression.[5] However, our study demonstrated that HU-R is a more reliable factor for disease progression in HU-R/I patients. Age at the time of HU-R/I development and lead time from diagnosis of PV to HU-R/I development were not significantly associated with disease progression or PFS.

According to the ELN criteria, it remains ambiguous whether the development of cytopenia, even at the minimal dose of HU required to achieve hematologic complete response, should be defined as resistance or intolerance.[12,16,18] Alvarez-Larrán et al.[13] independently evaluated each of the five ELN criteria of HU-R/I. They identified the clinical significance of developing cytopenia at the lowest dose of HU necessary for a response, which was associated with poorer survival as well as an increased risk of progression to both myelofibrosis and acute leukemia. In our study, patients who developed cytopenia were categorized into the resistance group, and the largest number of patients in the HU-R group met this criterion. Our findings also support their suggestion that the development of cytopenia should be categorized as resistance rather than intolerance.

Due to the limited number of patients in our study, we were unable to analyze the impact of individual criteria defining resistance and intolerance on clinical outcomes. The ELN introduced a unified definition of resistance and intolerance to HU in 2009,[16,18] but it was

later modified in clinical trials due to the dosing limitation of up to 2 g of HU in real-world patients.[15,22] The modified ELN criteria define the maximum tolerated dose as the threshold for resistance, rather than a fixed daily dose of 2 g of HU. Demuynck et al.[23] reported that 4.7% of patients met the criteria for resistance, and 16.0% met the criteria for intolerance according to the original ELN criteria. However, none of the patients in their study received a minimum dose of 2 g of HU per day. In contrast, when applying the modified ELN criteria, 23.6% of patients were classified as resistant, and 16.0% were categorized as intolerant. Similarly, we also observed that a daily dose of 2 g was not tolerable for most Asian patients, making it challenging to identify HU-R patients according to the original ELN criteria. These findings suggest that the maximum tolerated dose should be applied to define resistance in real-world patients, as in the modified ELN criteria.[14,24]

In conclusion, our findings indicate that patients with PV who developed HU-R demonstrated a higher incidence of disease progression and poorer survival outcomes compared to patients with HU-I. These results underscore the importance of accurately detecting HU-R in clinical decision-making pertaining to second-line treatment options. Given the limited availability of therapeutic choices, previous clinical studies typically included both resistant and intolerant patients for second-line therapeutics. However, our study suggests that future investigations examining treatment effects should consider differences in PFS and OS between the two patient groups, with the aim of mitigating thrombosis risk and altering the course of the disease.

REFERENCES

1. Vannucchi AM. Insights into the pathogenesis and management of thrombosis in polycythemia vera and essential thrombocythemia. *Intern Emerg Med* 2010;5(3):177-84. **PUBMED | CROSSREF**
2. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127(20):2391-405. **PUBMED | CROSSREF**
3. Moulard O, Mehta J, Fryzek J, Olivares R, Iqbal U, Mesa RA. Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union. *Eur J Haematol* 2014;92(4):289-97. **PUBMED | CROSSREF**
4. Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. *Leukemia* 2010;24(6):1128-38. **PUBMED | CROSSREF**
5. Tefferi A, Rumi E, Finazzi G, Gisslinger H, Vannucchi AM, Rodeghiero F, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia* 2013;27(9):1874-81. **PUBMED | CROSSREF**
6. Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol* 2005;23(10):2224-32. **PUBMED | CROSSREF**
7. Cerquozzi S, Tefferi A. Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. *Blood Cancer J* 2015;5(11):e366. **PUBMED | CROSSREF**
8. Finazzi G, Barbui T. Evidence and expertise in the management of polycythemia vera and essential thrombocythemia. *Leukemia* 2008;22(8):1494-502. **PUBMED | CROSSREF**
9. Marchetti M, Vannucchi AM, Griesshammer M, Harrison C, Koschmieder S, Gisslinger H, et al. Appropriate management of polycythaemia vera with cytoreductive drug therapy: European LeukemiaNet 2021 recommendations. *Lancet Haematol* 2022;9(4):e301-11. **PUBMED | CROSSREF**
10. Tefferi A, Vannucchi AM, Barbui T. Polycythemia vera: historical oversights, diagnostic details, and therapeutic views. *Leukemia* 2021;35(12):3339-51. **PUBMED | CROSSREF**
11. Antonioli E, Guglielmelli P, Pieri L, Finazzi M, Rumi E, Martinelli V, et al. Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN. *Am J Hematol* 2012;87(5):552-4. **PUBMED | CROSSREF**

12. Alvarez-Larrán A, Pereira A, Cervantes F, Arellano-Rodrigo E, Hernández-Boluda JC, Ferrer-Marín F, et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. *Blood* 2012;119(6):1363-9. **PUBMED** | **CROSSREF**

13. Alvarez-Larrán A, Kerguelen A, Hernández-Boluda JC, Pérez-Encinas M, Ferrer-Marín F, Bárez A, et al. Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythaemia vera. *Br J Haematol* 2016;172(5):786-93. **PUBMED** | **CROSSREF**

14. Parasuraman S, DiBonaventura M, Reith K, Naim A, Concialdi K, Sarlis NJ. Patterns of hydroxyurea use and clinical outcomes among patients with polycythemia vera in real-world clinical practice: a chart review. *Exp Hematol Oncol* 2016;5(1):3. **PUBMED** | **CROSSREF**

15. Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med* 2015;372(5):426-35. **PUBMED** | **CROSSREF**

16. Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch H, et al. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. *Br J Haematol* 2010;148(6):961-3. **PUBMED** | **CROSSREF**

17. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3(4):692-4. **PUBMED** | **CROSSREF**

18. Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29(6):761-70. **PUBMED** | **CROSSREF**

19. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med* 2013;368(1):22-33. **PUBMED** | **CROSSREF**

20. Alvarez-Larrán A, Díaz-González A, Such E, Mora E, Andrade-Campos M, García-Hernández C, et al. Genomic characterization of patients with polycythemia vera developing resistance to hydroxyurea. *Leukemia* 2021;35(2):623-7. **PUBMED** | **CROSSREF**

21. Tefferi A, Barraco D, Cerquozzi S, Lasho TL, Hanson CA, Ketterling RP, et al. Identification of serum lactate dehydrogenase (LDH) as an independent prognostic biomarker in polycythemia vera. *Blood* 2016;128(22):3111. **CROSSREF**

22. Passamonti F, Griesshammer M, Palandri F, Egyed M, Benevolo G, Devos T, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. *Lancet Oncol* 2017;18(1):88-99. **PUBMED** | **CROSSREF**

23. Demuynck T, Verhoef G, Delforge M, Vandenberghe P, Devos T. Polycythemia vera and hydroxyurea resistance/intolerance: a monocentric retrospective analysis. *Ann Hematol* 2019;98(6):1421-6. **PUBMED** | **CROSSREF**

24. McMullin MF, Wilkins BS, Harrison CN. Management of polycythaemia vera: a critical review of current data. *Br J Haematol* 2016;172(3):337-49. **PUBMED** | **CROSSREF**