Conventional interferon-α 2b *versus* hydroxyurea for newly-diagnosed patients with polycythemia vera in a real world setting: a retrospective study based on 286 patients from a single center

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by clonal proliferation of multipotent bone marrow progenitors.[1] A clinical trial investigating the efficacy of pegylated interferon (IFN) for PV and essential thrombocytosis is ongoing in China. However, as only conventional IFN and hydroxyurea (HU) are covered by Chinese basic medical insurance, these cytoreductive agents are recommended as first-line treatment by the consensus of Chinese experts for the diagnosis and treatment of PV, including low-risk patients.[2]

As the difference in efficacy between conventional IFN and HU for newly-diagnosed PV is undefined, we retrospectively analyzed data of 286 newly-diagnosed PV patients who were treated at the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences between June 1, 2007 and February 28, 2020. All patients received conventional IFN-α 2b or HU for at least 6 months. Patients were excluded if they changed groups. The flowchart for patient selection is shown in the *Online Supplementary Figure S1A*. Cases were diagnosed in accordance with the 2016 World Health Organization diagnostic definitions.[3]

Conventional IFN-α 2b was recommended first for young (age <60 years old) patients and older patients without contraindications. HU was usually recommended for other patients. In total, 82 and 204 patients received single-agent conventional IFN-α 2b (IFN cohort) and single-agent HU (HU cohort), respectively. Generally, the initial dose of conventional IFN-α 2b was 3×10^6 IU three times per week; the initial dose of HU was 20 mg/kg/day. Treatment schedules were adjusted by monitoring peripheral blood counts with the target of hematocrit (HCT) <45%.

Quantitative measurements of the *JAK2* V617F variant allele frequency (VAF) were performed by real-time polymerase chain reaction (PCR) as previously described.[4] Hematologic and molecular responses were evaluated in accordance with the revised response criteria of the European LeukemiaNet (ELN) and International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT).[5] Complete hematologic remission (CHR) was defined as HCT <45% without phlebotomy, white blood cell (WBC) $<10\times10^9$/L, and platelets $\leq400\times10^9$/L. Complete molecular response (CMR) was defined as indetectable *JAK2* V617F mutation. Partial molecular response (PMR) applied only to patients with a *JAK2* V617F VAF ≥20% before treatment and was defined as a ≥50% decrease in allele burden after treatment.[5]

The clinical and laboratory features of subjects in the IFN and HU cohorts are displayed in Table 1. The median treatment duration in the IFN and HU cohorts were 51 months (interquartile range [IQR], 24–83 months) and 53 months (IQR, 31–84 months), respectively. The duration of exposure to IFN or HU for each patient is shown in the *Online Supplementary Figure S1B* and *C*.

Compared with the HU cohort, a higher proportion of patients in the IFN cohort achieved CHR (65% *vs*. 43%; *P*=0.001), control of HCT (72% *vs*. 43%; *P*=0.06), control of platelets (88% *vs*. 77%; *P*=0.04), and control of WBC (89% *vs*. 72%; *P*=0.002; Figure 1A) during follow-up.

A higher proportion of low-risk subjects who received IFN achieved CHR compared with those who received HU (64% *vs*. 32%; *P*=0.001; Figure 2A). Consistently, high-risk subjects who received IFN also had a higher CHR rate than those who received single-agent HU (68% *vs*. 47%; *P*=0.06; Figure 2C).

Interestingly, the median increase in mean corpuscular volume (MCV) from baseline, when patients achieved the best control of HCT, was 21.2 fL (IQR, 9.1–31.9 fL) in the HU cohort, which was much higher than in the IFN cohort (3.9 fL; IQR, –2.8–9.5; *P*<0.001). Because HCT equals the erythrocyte count multiplied by MCV, some patients in the HU cohort might have been phlebotomized with normal RBC.

The median duration from starting treatment to achiev-

Table 1. Clinical features of the interferon and hydroxyurea cohorts at baseline.

Variables	IFN (N = 82)	HU (N = 204)	*P*-value
Age, years	51 (44-57)	61 (52-67)	<0.001
Sex, female	50 (61%)	104 (51%)	0.13
Palpable splenomegaly	20 (26%)	52 (27%)	0.83
Disease duration, month; median (range)	0 (0-2)	0 (0-2)	0.31
Baseline hemoglobin, g/L	189 (177-209)	197 (187-210)	0.01
Baseline RBC, $\times10^{12}$/L	7.0 (6.3-7.6)	7.2 (6.5-7.8)	0.02
Baseline hematocrit, %	58 (54-63)	61 (57-65)	0.003
Baseline WBC, $\times10^9$/L	12.6 (9.4-15.1)	13.1 (9.8-18.1)	0.15
Baseline platelet, $\times10^9$/L	464 (339-623)	424 (324-572)	0.40
Baseline MCV, fL	84.0 (80.7-89.6)	85.4 (79.8-89.9)	0.99
JAK2 V617F mutation	77 (94%)	191 (94%)	0.93
Baseline *JAK2* V617F VAF, %, (n=209)*	56 (35-73)	59 (33-73)	0.62
Abnormal cytogenetics, % (n/N)	4% (2/49)	4% (4/114)	1.00
Thrombosis pretreatment (n=406)	23 (29%)	69 (35%)	0.36
Thrombosis risk stratification (n=406)			<0.001
Low risk	52 (65%)	59 (30%)	
High risk	28 (35%)	141 (70%)	
Follow-up from start of treatment, months	52 (35-91)	55 (33-84)	0.82

Data are presented as median (interquartile range [IQR]) or n (%), unless otherwise indicated. IFN: interferon; HU: hydroxyurea; RBC: red blood cell; WBC: white blood cell; MCV: median corpuscular volume; VAF: variant allele frequency; *JAK2* V617F VAF in *JAK2* V617F-mutated patients.

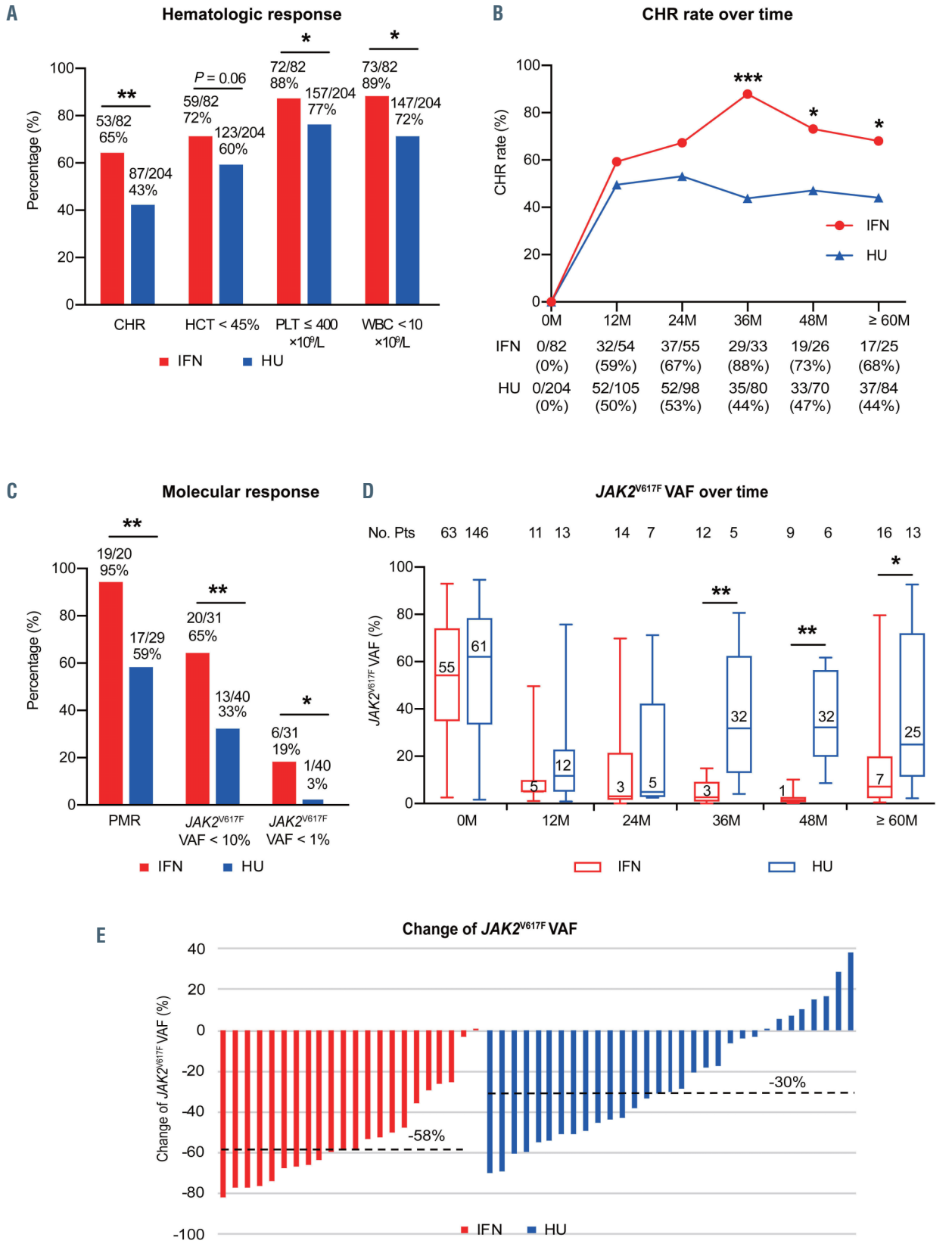

Figure 1. Comparison of hematologic and molecular responses between the interferon and hydroxyurea cohorts. (A) Hematologic responses, (B) complete hematologic remission (CHR) rates over time, (C) molecular responses, and (D) dynamics of *JAK2* V617F variant allele frequencies (VAF) over time are compared between the interferon (IFN) and hydroxyuera (HU) cohorts. In (D) the horizontal lines indicate median values; bars represent minimum and maximum values; boxes represent values included between the 25% and 75% percentiles. (E) *JAK2v* V617F VAF waterfall plot in the IFN (n=22) and HU (n=31) cohorts; the y-axis indicates the absolute change of the *JAK2* V617F VAF from baseline to the best molecular response; each bar represents a patient; dotted lines represent median changes of the *JAK2* V617F VAF in each group. IFN: conventional (non-pegylated) interferon; HCT: hematocrit; PLT: platelet; WBC: white blood cell; PMR: partial molecular response; Pts: patients. *P<0.05; **P<0.01; ***P<0.001.

ing CHR was 11 months (IQR, 7–23 months) in the IFN cohort, which was shorter than in the HU cohort (19 months; IQR, 10–47 months; *P*=0.001). Among the patients who achieved CHR, two (4%) and seven (7%) were lost during follow-up in the IFN and HU cohorts, respectively. Compared with the HU cohort, CHR rates in the IFN cohort were higher throughout the treatment duration and became significantly better after 3 years of continuous treatment (88% *vs*. 44%; *P*<0.001; Figure 1B), which was consistent with the results of the PROUD-PV and CONTINUATION-PV studies, which used pegylated IFN.[6]

In addition to hematologic responses, the IFN cohort also showed better molecular responses than the HU cohort. In total, 31 and 40 patients had data regarding molecular responses in the IFN and HU cohorts, respectively. The median *JAK2* V617F VAF at baseline were not significantly different between the IFN and HU cohorts (68% [IQR, 51–78%] *vs*. 62% [IQR, 40–70%]; *P*=0.21). Only one patient in the IFN cohort achieved CMR. The percentage of patients who obtained a *JAK2* V617F VAF <10% was higher in the IFN (65%) than in the HU (33%) cohort (*P*=0.007; Figure 1C). Among patients with baseline JAK2 VAFs ≥20%, 95% (19/20) achieved PMR in the IFN and 59% (17/29) in the HU cohorts (*P*=0.007; Figure 1C). The median change in *JAK2* V617F VAF from baseline to the best molecular response in the IFN and HU cohorts was −58% (IQR, −69% to −34%) and −30% (IQR, −51% to −0.4%) (*P*=0.001; Figure 1E). Finally, the *JAK2* V617F VAF in the IFN cohort was significantly lower than in the HU cohort after 3 years of continuous treatment (Figure 1D).

Because the IFN cohort was younger than the HU cohort, we compared treatment responses between patients in the IFN and HU cohorts matched for age and sex. The baseline peripheral blood counts, *JAK2* V617F allele burdens, follow-ups, and thrombosis risk stratifications were balanced between the two matched cohorts (*Online Supplementary Figure S2A*). The CHR rate (66% [44/67] *vs*. 34% [23/67]; *P*=0.001; *Online Supplementary Figure S2B*), control of HCT rate (73% [49/67] *vs*. 54% [36/67]; *P*=0.03; *Online Supplementary Figure S2B*), and

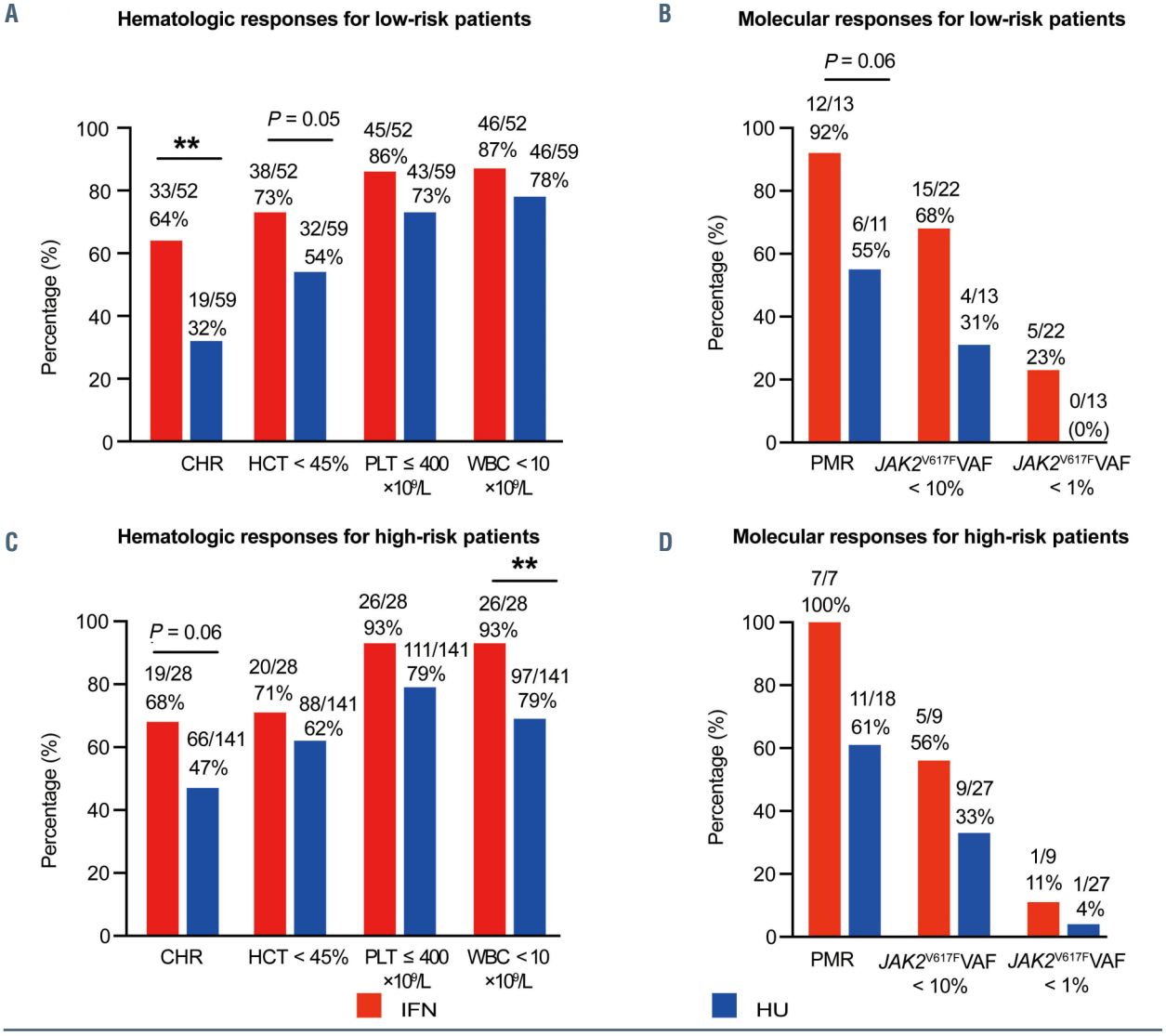

Figure 2. Comparison of hematologic and molecular responses between the interferon and hydroxyurea cohorts stratified by thrombosis risk. Hematologic (A) and molecular (B) responses of low-risk patients. Hematologic (C) and molecular (D) responses of high-risk patients. IFN: interferon; HU: hydroxyurea; RBC: red blood cell; WBC: white blood cell; HCT: hematocrit; PLT: platelet; VAF: variant allele frequency; IQR: interquartile range; **JAK2* V617F VAF in *JAK2* V617F-mutated patients; CHR: complete hematologic remission; PMR: partial molecular response. **P*<0.05; ***P*<0.01; ****P*<0.001.

PMR rate (95% [18/19] *vs*. 62% [8/13]; *P*=0.029; *Online Supplementary Figure S2C*) were significantly higher in the IFN cohort than in the HU cohort when matched for age and sex. When patients were stratified by thrombosis-risk, the CHR rate in the IFN cohort was higher than in the HU cohort for age- and sex-matched low-risk (63% [24/38] *vs*. 26% [9/35]; *P*=0.002) and high-risk (70% [19/27] *vs*. 45% [14/31]; *P*=0.067) patients.

In total, 14 of 82 subjects (17%) discontinued IFN treatment for the following reasons: normalized peripheral blood counts (n=8, 57%), adverse effects (n=2, 14%), disease progression (n=1, 7%), and unknown reasons (n=3, 21%). Fever was the most common adverse effect of IFN, which was reported in 23% (14/62) of patients, followed by bone pain in 11% (7/62) of patients.

Post-treatment thrombotic events occurred in two (2%) and six (3%) patients in the IFN and HU cohorts. The thrombosis rates were 0.5% (95% confidence interval [CI]: 0–1.1) patients per year for the IFN cohort and 0.7% (95% CI: 0.2–1.2) for the HU cohort. These rates were much lower than those published in a previous study (2.62%; 95% CI: 2.34–2.94 patients per year).[7] In our study, the thrombosis rate in the low-risk cohort (95% CI: 0.6% [0.2–0.9]) was lower than that of low-risk PV patients treated by phlebotomy, as reported by Barbui *et al.* (95% CI: 2.0% [1.5-2.5]).[8]

The lower incidence of thrombosis in this study compared with previous studies might be related to racial differences in thromboembolism between Asian and Western populations. This is related to differences in genetic polymorphisms and environmental factors, such as obesity and healthcare facilities.[9,10] For instance, a study reported that Japanese patients with paroxysmal nocturnal hemoglobinuria (PNH) had a significantly lower incidence of thrombosis than American PNH patients.[11] Moreover, the ECLAP study and a matched study of 951 patients with PV reported a benefit-risk profile of HU therapy over phlebotomy with respect to the lower rate of arterial thrombosis.[12,13] Our findings suggested that early intervention with cytoreductive treatments for low-risk subjects rather than phlebotomy might also correlate with lower thrombosis rates.

Thrombosis-free survival rates were not significantly different between the IFN and HU cohorts (*P*=0.81), similar results were found when adjusted by age (*P*=0.73; *Online Supplementary Figure S3A*). There was no significant difference in overall survival (*P*=0.99; *Online Supplementary Figure S3B*) or myelofibrosis-free survival (*P*=0.98; *Online Supplementary Figure S3C*) between the IFN and HU cohorts when adjusted by age. A previous retrospective study of PV patients reported that IFN reduced the risk of mortality and transformation into myelofibrosis compared with HU or phlebotomy.[14] The different conclusions that we report might be due to the relatively short follow-up in our study. Finally, there was no significant difference in thrombosis-free survival (*P*=0.40), overall survival (*P*=0.55), or myelofibrosis-free survival (*P*=0.26) between patients who achieved PMR or not.

A recent meta-analysis reported that CHR rates, thrombotic complications, and treatment discontinuations owing to adverse events were not significantly different between pegylated and conventional IFN.[15] In our study, conventional IFN-α 2b was a good choice for PV, showing better efficacy than HU and acceptable tolerance.

In conclusion, this study found that the hematologic and molecular responses of newly-diagnosed PV to conventional IFN-α 2b were better than to HU. There are limitations to this study, such as it being a retrospective study from a single center with a short follow-up, a mixture of low- and high-risk patients, and only a few patients who were tested for molecular responses, which are all sources of potential bias.

Dan Liu,[1,2] Zefeng Xu,[1,2*] Peihong Zhang,[1,3] Tiejun Qin,[1,2] Xiujuan Sun,[1] Shiqiang Qu,[1,2] Lijuan Pan,[1,2] Jiao Ma,[1,3] Wenyu Cai,[1,3] Jinqin Liu,[1] Huijun Wang,[1,3] Qi Sun,[1,3] Zhongxun Shi,[1,2] Huijun Huang,[1,2] Gang Huang,[4] Robert Peter Gale,[5] Bing Li,[1,2] Raajit K. Rampal [6] and Zhijian Xiao[1,2,3]*

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [2]MDS and MPN Center, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [3]Hematologic Pathology Center, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [4]Divisions of Experimental Hematology and Cancer Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [5]Hematology Section, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, UK and [6]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

**DL and ZX contributed equally as co-first authors.*

Correspondence:
BING LI - libing@ihcams.ac.cn
RAAJIT K RAMPAL - rampalr@mskcc.org
ZHIJIAN XIAO - zjxiao@ihcams.ac.cn

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Contributions: ZJX designed the study; DL and ZFX collected and interpreted the data and performed statistical analysis; PHZ and QS contributed to analysis of bone marrow histology; TJQ, SQQ, LJP, WYC, JQL, HJW, XJS, MJ, and QYG contributed to recruiting patients and collecting data; DL wrote the manuscript with contributions from ZJX, ZFX, BL, GH, RPG, RKR, ZXS, and HJH. All authors reviewed the manuscript during its preparation and approved the final version of the manuscript.

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References

1. Grinfeld J, Nangalia J, Baxter EJ, et al. Classification and personalized prognosis in myeloproliferative neoplasms. N Engl J Med. 2018;379(15):1416-1430.
2. Leukemia and Lymphoma Group, Chinese Society of Hematology,

Chinese Medical Association. [Chinese expert consensus on the diagnosis and treatment of polycythemia vera (2016)]. Zhonghua Xue Ye Xue Za Zhi. 2016;4(4):265-268.
3. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.
4. Tashi T, Swierczek S, Kim SJ, et al. Pegylated interferon Alfa-2a and hydroxyurea in polycythemia vera and essential thrombocythemia: differential cellular and molecular responses. Leukemia. 2018;32(8):1830-1833.
5. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood. 2013;121(23):4778-4781.
6. Gisslinger H, Klade C, Georgiev P, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020;7(3):e196-e208.
7. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. Leukemia. 2013;27(9):1874-1881.
8. Barbui T, Vannucchi AM, Carobbio A, et al. The effect of arterial hypertension on thrombosis in low-risk polycythemia vera. Am J Hematol. 2017;92(1):E5-E6.
9. Hamasaki N, Kuma H, Tsuda H. Activated protein C anticoagulant system dysfunction and thrombophilia in Asia. Ann Lab Med. 2013;33(1):8-13.
10. Zakai NA, McClure LA. Racial differences in venous thromboembolism. J Thromb Haemost. 2011;9(10):1877-1882.
11. Nishimura JI, Kanakura Y, Ware RE, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. Medicine (Baltimore). 2004;83(3):193-207.
12. Barbui T, Vannucchi AM, Finazzi G, et al. A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera: a propensity-matched study. Am J Hematol. 2017;92(11):1131-1136.
13. Barbui T, De Stefano V, Ghirardi A, et al. Different effect of hydroxyurea and phlebotomy on prevention of arterial and venous thrombosis in polycythemia vera. Blood Cancer J. 2018;8(12):124.
14. Abu-Zeinah G, Krichevsky S, Cruz T, et al. Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival. Leukemia. 2021;35(9):2592-2601.
15. Bewersdorf JP, Giri S, Wang R, et al. Interferon alpha therapy in essential thrombocythemia and polycythemia vera - a systematic review and meta-analysis. Leukemia. 2020;35(6):1643-1660.