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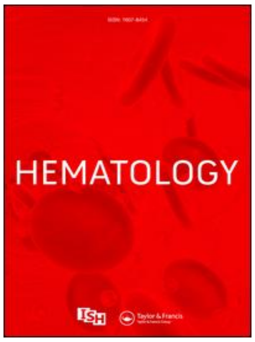

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Myeloproliferative neoplasms treated with hydroxyurea, pegylated interferon alpha-2A or ruxolitinib: clinicohematologic responses, quality-of-life changes and safety in the real-world setting

Harinder Gill[a], Garret M.K. Leung[a], Rita Yim [a], Paul Lee [a], Herbert H. Pang[b], Ho-Wan Ip[c], Rock Y.Y. Leung[c], Jun Li [d,e], Gianni Panagiotou[e,f,g], Edmond S.K. Ma[h] and Yok-Lam Kwong[a]

[a]Department of Medicine, The University of Hong Kong, Hong Kong, People's Republic of China; [b]School of Public Health, The University of Hong Kong, Hong Kong, People's Republic of China; [c]Department of Pathology, Queen Mary Hospital, Hong Kong, People's Republic of China; [d]Department of Infectious Diseases and Public Health, The City University of Hong Kong, Hong Kong, People's Republic of China; [e]School of Biological Sciences, The University of Hong Kong, Hong Kong, People's Republic of China; [f]Department of Microbiology, The University of Hong Kong, Hong Kong, People's Republic of China; [g]Department of Systems Biology and Bioinformatics, Leibniz Institute for Natural Product Research and Infection Biology, Hans Knöll Institute (HKI), Jena, Germany; [h]Department of Pathology, Hong Kong Sanatorium and Hospital, Hong Kong, People's Republic of China

ABSTRACT

Introduction: Real-world data of responses, quality-of-life (QOL) changes and adverse events in patients with myeloproliferative neoplasms (MPN) on conventional therapy (hydroxyurea ± anagrelide), pegylated interferon alpha-2A (PEG-IFNα-2A) or ruxolitinib are limited.
Methods: We prospectively studied MPN patients receiving conventional therapy, PEG-IFNα-2A or ruxolitinib. Next-generation sequencing of 69 myeloid-related genes was performed. Clinicohematologic responses, adverse events, and QOL (determined by the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score, MPN-SAF TSS) were evaluated.
Results: Seventy men and fifty-five women with polycythemia vera (PV) ($N = 23$), essential thrombocythemia (ET) ($N = 56$) and myelofibrosis (MF) ($N = 46$) were studied for a median of 36 (range: 19–42) months. In PV, responses were comparable for different modalities. *CREBBP* mutations were associated with inferior responses. In ET, PEG-IFNα-2A resulted in superior clinicohematologic complete responses (CHCR) ($P = 0.045$). In MF, superior overall response rates (ORR) were associated with ruxolintib ($P = 0.018$) and *JAK2*V617F mutation ($P = 0.04$). For the whole cohort, ruxolitinib led to rapid and sustained reduction in spleen size within the first 6 months, and significant improvement of QOL as reflected by reduction in MPN-SAF TSS ($P < 0.001$). Adverse events of grades 1–2 were observed in 44%, 62% and 20% of patients receiving conventional therapy, PEG-IFNα-2A and ruxolitinib respectively; and of grade 3–4 in 7% and 9% of patients receiving PEG-IFNα-2A and ruxolitinib.
Conclusions: Conventional therapy, PEG-IFNα-2A and ruxolitinib induced responses in all MPN subtypes. PEG-IFNα-2A led to superior CHCR in ET; whereas ruxolitinib resulted in superior ORR in MF, and significant reduction in spleen size and improvement in QOL.

KEYWORDS
Myeloproliferative neoplasms; polycythemia vera; essential thrombocythemia; primary myelofibrosis; hydroxyurea; anagrelide; interferon; ruxolitinib

Introduction

For patients with myeloproliferative neoplasms (MPN) requiring cytoreduction, hydroxyurea has been the conventional first-line treatment [1–3]. An alternative therapy is long-acting pegylated interferon alpha (PEG-IFNα), which not only achieves high rates of hematologic response, but may also act on the neoplastic stem cells, thereby inducing molecular responses [4–11]. PEG-IFNα is now considered an appropriate first-line treatment for young patients with polycythemia vera (PV), and second-line therapy in patients resistant or intolerant to hydroxyurea [3,12–15]. Prospective trial data of PEG-IFNα have mainly been on PV and essential thrombocythemia (ET) [11,16], but limited in primary myelofibrosis (PMF). The JAK1/JAK2 inhibitor ruxolitinib [17] has shown results superior to standard therapy in phase 3 trials in patients with MF and PV [18–21].

Although PEG-IFNα and ruxolitinib appear promising in clinical trials of MPN, they have not been prospectively compared with conventional therapy in a non-trial real-world setting. In this study, we prospectively evaluated the efficacy and safety of PEG-IFNα-2A, ruxolitinib and hydroxyurea in a cohort of MPN patients.

Patients and methods

Patients and study design. This was a prospective cohort study. Patients with PV, ET, PMF, post-PV myelofibrois (PPV-MF) and post-ET myelofibrosis (PET-MF) [22, 23],

CONTACT Yok-Lam Kwong ylkwong@hkucc.hku.hk
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who received hydroxyurea, PEG-IFNα-2A or ruxolitinib were recruited. All cases were diagnosed according to the World Health Organization (WHO) 2016 criteria. For cases presenting before 2016, all materials were reviewed to ensure that the diagnoses complied with the WHO 2016 criteria. Baseline clinicopathologic and molecular characteristics were determined. Prospective data on treatment responses, quality-of-life (QOL) and adverse events were obtained every 2–4 weeks for the first 6 months and every 3 months thereafter. This study was approved by the institutional review board and registered at the HKU Clinical Trial Registry (Identifier: HKUCTR-2030). Patients gave written informed consent.

Molecular studies and next-generation sequencing (NGS). Patients were annotated for driver mutations of *JAK2*, *CALR* and *MPL* as previously described [24–29]. Targeted NGS was performed on archived DNA from diagnostic bone marrow samples. A custom xGen Lockdown Panel targeting 69 myeloid-relevant genes (supplemental file 1) was designed based on GRCh37/hg19 (Integrated DNA Technologies, Coralville, Iowa, USA). All exons of the 69 genes were sequenced, with a total of 2885 probes covering 273.03 kb. The enriched libraries were sequenced pair-ended with the Illumina MiSeq System (Illumina, San Diego, California, USA). FASTQ files containing at least 1 million raw reads with coverage of 500X were generated for bioinformatic analyses as previously described [30].

Treatment. The choice of conventional therapy, PEG-IFNα-2A or ruxolitinib was based on prevailing guidelines [1,3,31], physician choice and patient preferences. We also took into account concomitant medical comorbidities that would increase cardiovascular risks, including smoking, hypertension, hyperlipidemia, type 2 diabetes mellitus, a strong family history of cardiovascular diseases and presence of vascular symptoms for initiation and choice of treatment. Conventional therapy included hydroxyurea for cytoreduction and anagrelide as an adjunct for platelet control. PEG-IFNα-2A was recommended as first-line treatment for MPN patients aged ≤50 years, or as second-line therapy for patients resistant or intolerant to hydroxyurea. It was started at 135 µg subcutaneously, initially every 2 weeks and escalated to weekly. Ruxolitinib was recommended for patients with constitutional symptoms, symptomatic splenomegaly, and intolerance or resistance to hydroxyurea [1]. It was started at 10 mg twice daily and escalated by 10 mg/day every 4 weeks to a maximum of 25 mg twice daily. PEG-IFNα-2A or ruxolitinib was withheld in the event of ≥ grade 3 hematologic or non-hematologic toxicities, and resumed on resolution of toxicities. All patients received anti-platelet therapy with low-dose aspirin (80 mg/day) or clopidogrel (75 mg/day) if sensitive to aspirin. The target hematocrit was <45% for PV. The target platelet count was 180–450 × 10^9/L for PV and ET [3,31–33]. In MF, the threshold for blood transfusion in asymptomatic patients without cardiac comorbidities was 7 g/dL. During ruxolitinib therapy, patients positive for hepatitis B virus (HBV) surface antigen (HBsAg) received entecavir 0.5 mg/day as prophylaxis; whereas patients negative for HBsAg but positive for anti-hepatitis B core antigen–antibody (anti-HBc) were regularly monitored for circulating HBV DNA, and started on entecavir once HBV DNA became detectable [34]. All patients gave informed consent to treatment. Patients treated with hydroxyurea or anagrelide prior to this study were not excluded. Off-label use of ruxolitinib was allowed with written informed consent for ET patients with significant symptoms, who refused other treatment options.

Definitions. Risk stratification was conducted as follows: International Prognostic Scoring System (IPSS) [32] and European LeukemiaNet (ELN) recommendations [1] for PV; International Prognostic Score for ET (IPSET) [35] and the IPSET-thrombosis scores [36] for ET; and Dynamic International Prognostic Scoring System (DIPSS) [37] and DIPSS-plus [38] for MF. Treatment responses (clinicohematologic complete response, CHCR; partial response, PR; stable disease, SD; clinical improvement, CI; progressive disease, PD; no response, NR) were defined according to the criteria proposed by the ELN and International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) [39–41] (supplemental file 2). Spleen size was defined as the distance from the costal margin to the spleen tip, verified by two independent clinicians. Quality of life (QOL) was evaluated by a Chinese version of the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), which consisted of 10 items for symptom burden on a 0–10 scale [42]. Adverse events (AE) were determined and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [43].

Sample size calculation. To give power of at least 80% (2-sided alpha level of 0.05) to detect ≥20% difference in the outcomes between various treatment groups, it was estimated that a sample size of 108 patients (36 patients per treatment group) would be required.

Statistical analyses. All data were censored on 30 June 2019. Categorical variables were analyzed with the χ^2 test. Continuous variables were analyzed with non-parametric tests. Clinico-hematologic and QOL responses of different treatment modalities (conventional *versus* ruxolitinib *versus* PEG-IFNα-2A) were assessed at 3-monthly time points, and compared with one-way analysis of covariance (ANCOVA), incorporating baseline values as a covariate to ensure that differences at different time points were unaffected by baseline inter-group variations. Graphs and charts were constructed using Graphpad Prism version 7.02 and R software (R Project for Statistical Computing, Vienna, Austria). Concentration graph analysis was used to determine the gene relevance network, generating a covariance matrix for Circos plot (Circos software). Statistical analyses were performed using SPSS version 25.0 (Chicago, IL, USA). *P*-values (2-tailed) of <0.05 were considered significant.

Results

Patients. Seventy-five men and fifty-five women (PV, $N = 23$; ET, $N = 56$; MF, $N = 46$) at a median age of 48.4 (range: 22.7–88.6) years were recruited (Table 1). None of our pre-MF patients required treatment during the study period and so they were not included. The median duration of follow-up for the cohort was 36.1 (range: 19–42) months. The median durations of treatment were 20 (range: 2–24) months for hydroxyurea, 16 (range: 1.5–24) months for PEG-IFNα-2A, and 12 (range: 1.1–24) months for ruxolitinib. Gene mutations were detected in 122 (98%) patients by NGS (Figure 1, supplemental file 3). Three patients had no mutations detected but fulfilled morphologic criteria for MPN. Cytogenetic studies were performed in 97 patients with 22 patients (23%) showing abnormal karyotypes (supplemental file 4).

Clinicopathologic and NGS features of PV. There were 15 men and 8 women, at a median age of 51 (range: 34–89) years. At recruitment, 19 patients (83%) had prior treatment with hydroxyurea, with median hemoglobin and hematocrit of 15.4 (range: 11.2–22.1) g/dL and 0.43 (range: 0.32–0.66) respectively. IPSS risk scores were low ($N = 16$, 70%), intermediate ($N = 2$, 9%) and high ($N = 5$, 22%). ELN risk scores for thrombosis were low ($N = 17$, 74%) and high ($N = 6$, 26%). All cases tested positive for the *JAK2*V617F mutation. Other frequently mutated genes included *KMT2D* ($N = 5$, 22%), *ASXL1* ($N = 5$, 22%), *TET2* ($N = 4$, 17%) and *KMT2B* ($N = 4$, 17%) (Figure 1, supplemental file 5). Variant allele frequencies (VAF) of mutated genes and co-occurring mutations were shown in supplemental file 5.

Treatment and outcome in PV. Amongst treatment groups (conventional, PEG-IFNα-2A, ruxolitinib), the gender, age, hemoglobin, hematocrit, platelet count, lactate dehydrogenase (LDH), and splenomegaly were comparable. However, the ruxolitinib group showed a higher leucocyte count ($P = 0.009$), higher LDH ($P = 0.02$) and more patient belonging to high-risk categories (IPSS, $P = 0.009$; ELN, $P = 0.005$) (supplemental file 6). All patients were assessed for treatment responses (Table 2, Figure 2). At a median treatment duration at 6 (range: 3–18) months, the overall response rate (ORR) was 82% (CHCR: 52%; PR: 30%), which was comparable for various treatment groups. For genes in the NGS panel, only *CREBBP* mutations were associated with an inferior ORR ($P = 0.04$) (supplemental file 7). The hemoglobin fell in all groups, with the ruxolitinib group showing the lowest median hemoglobin, which at 15 months was significantly lower than the two other groups ($P = 0.03$) (Figure 2). The leucocyte and platelet counts also fell, except in the ruxolitinib group where the platelet count increased progressively during follow-up (Figure 2). There were no cardiovascular or thrombotic complications. One patient who received hydroxyurea for ten years prior to this study progressed to post-PV MF. Another patient with del(5)(q14q33) progressed to secondary acute myeloid leukemia (AML) with complex karyotypes 8 months after ruxolitinib treatment and 7 years after initial diagnosis.

Clinicopathologic and NGS features of ET. There were 30 men and 26 women, at a median age of 44.1 (range: 22.6–77.6) years. The median platelet count was 479 (range: 267–1500) $\times 10^9$/L. For the cohort, IPSET risk scores were low ($N = 40$, 71%), intermediate ($N = 15$, 27%) and high ($N = 1$, 2%), and IPSET-thrombosis risk scores were low/very low ($N = 44$, 79%), intermediate ($N = 1$, 2%) and high ($N = 11$, 20%). *JAK2*V617F mutation

Table 1. Clinicopathologic and treatment characteristics of 125 patients with myeloproliferative neoplasm.

	PV	ET	MF
Number of patients	23	56	46
Gender, number (%)			
Female	8 (35)	26 (46)	21 (46)
Male	15 (65)	30 (54)	25 (54)
Parameters at recruitment			
Age, years, median (range)	50.5 (33.7–88.6)	44.1 (22.6–77.6)	58.9 (32.1–81.1)
Hemoglobin, g/dL, median (range)	15.4 (11.2–22.1)	13.7 (8.9–16.9)	10.8 (6.7–17.1)
Hematocrit, %, median (range)	0.43 (0.32–0.66)	0.40 (0.27–0.50)	0.33 (0.20–0.55)
Leucocyte count, $\times 10^9$/L, median (range)	8.2 (4.1–26.3)	6.5 (1.5–20.2)	12.4 (3.7–44.4)
Platelet count, $\times 10^9$/L, median (range)	408 (154–751)	479 (267–1500)	375 (16–1682)
Lactate dehydrogenase, IU/L, median (range)	252 (161–597)	211 (154–374)	446 (147–1896)
Circulating blasts, %, median (range)	0	0	1 (0–8)
Prior splenectomy, number (%)	0	0	4 (9)
Splenomegaly, number (%)	4 (17)	5 (9)	32 (70)
Spleen size, cm, median (range)	4 (3–6)	3 (1–4)	5 (1–30)
Treatment, number (%)			
Hydroxyurea +/- anagrelide	9 (39)	22 (39)	4 (9)
Pegylated-interferon α-2A	9 (39)	27 (48)	19 (41)
Ruxolitinib	5 (22)	7 (13)	23 (50)

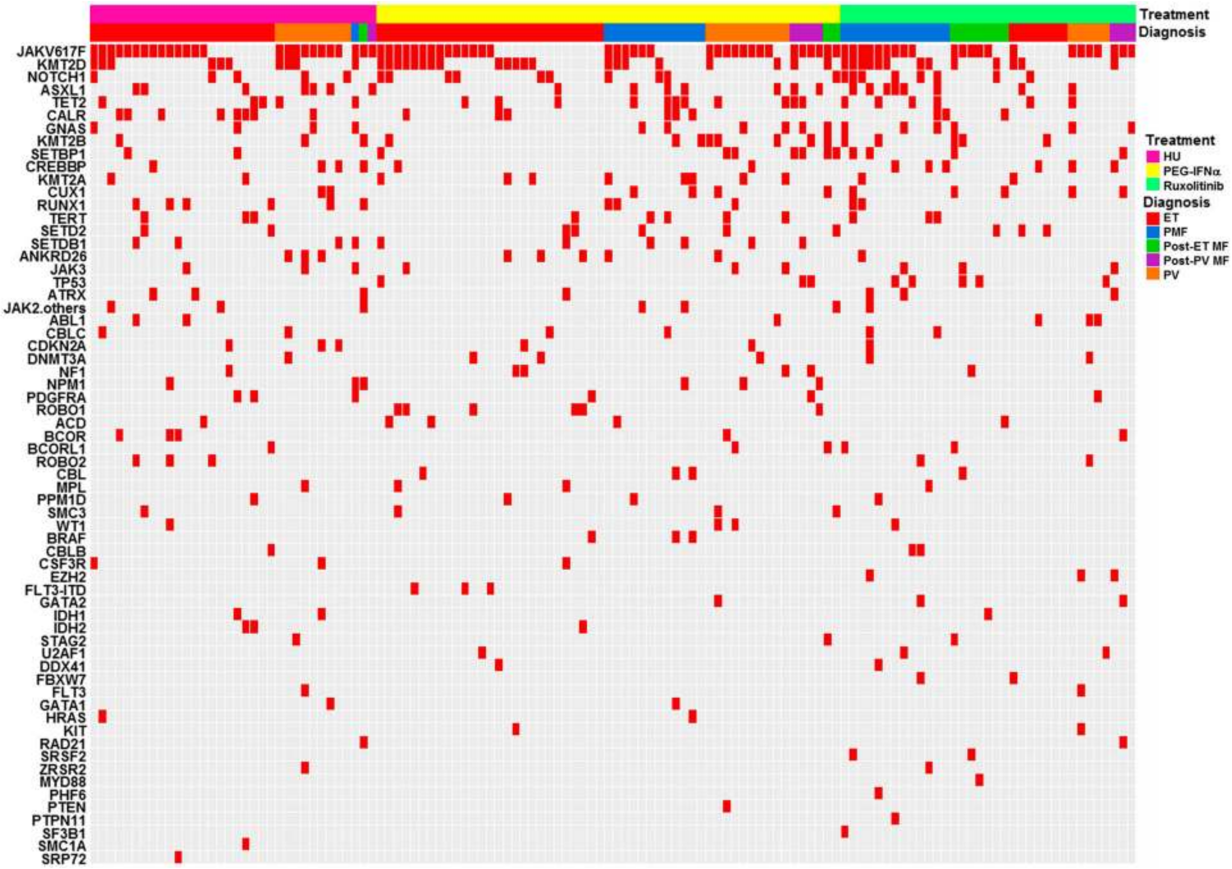

Figure 1. Heatmap showing frequency of gene mutations in each disease and treatment subgroup.

was present in 29 patients (52%). Other frequently mutated genes included *KMT2D* ($N = 21$, 38%), *NOTCH1* ($N = 10$, 18%), *CALR* ($N = 10$, 18%) and *TET2* ($N = 7$, 13%). *MPL* mutations were infrequently seen ($N = 2$, 4%) (Figure 1, supplemental file 8). VAF of mutated genes and co-occurring mutations were shown in supplemental file 8.

Treatment and outcome in ET. Amongst treatment groups, the gender, age, hemoglobin, hematocrit, WBC, LDH, IPSET score, and IPSET-thrombosis score were comparable. However, the ruxolitinib group had significantly more patients with splenomegaly ($P = 0.003$) (supplemental file 9). There was a trend towards a higher baseline platelet count in patients on ruxolitinib ($P = 0.053$). All patients were assessed for responses (Table 2, Figure 3). At a median treatment duration of 6 (range: 3–24) months, the ORR was 99% (CHCR: 79%; PR: 20%). PEG-IFNα-2A resulted in significantly higher CHCR than hydroxyurea or ruxolitinib (89% *versus* 77% *versus* 43%, $P = 0.045$). Genetic mutations did not impact on outcome (supplemental file 7). Ruxolitinib treatment resulted in significantly lower hemoglobin and hematocrit as compared with hydroxyurea and PEG-IFNα-2A ($P < 0.05$ from 12 months onwards for both hemoglobin and hematocrit). PEG-IFNα-2A resulted in the lowest median platelet count, which was significantly lower than the other groups from 9 months onwards ($P < 0.05$). There were no cardiovascular/thrombotic complications and disease progression during the follow-up period.

Clinicopathologic and NGS features of MF. There were 17 men and 10 women with primary MF (PMF) (59%); 5 men and 4 women with post-PV MF (19%); and 3 men and 7 women with post-ET MF (22%). For the whole

Table 2. Treatment responses in 125 patient myeloproliferative neoplasms.

		Treatment		
	All	Hydroxyurea	PEG-IFNα-2A	Ruxolitinib
Polycythemia vera				
Number of patients	23	9	9	5
Responses, number (%)				
CHCR	12 (52)	6 (67)	5 (56)	1 (20)
PR	7 (30)	2 (22)	3 (33)	2 (40)
NR	2 (9)	0 (0)	1 (11)	1 (20)
PD	2 (9)	1 (11)	0 (0)	1 (20)
Essential thrombocythemia				
Number of patients	56	22	27	7
Response, number (%)				
CHCR	44 (79)	17 (77)	24 (89)	3 (43)
PR	11 (20)	5 (23)	2 (7)	4 (57)
NR	1 (2)	0 (0)	1 (4)	0 (0)
PD	0 (0)	0 (0)	0 (0)	0 (0)
Myelofibrosis				
Number of patients	46	4	19	23
Response, number (%)				
CR	0 (0)	0 (0)	0 (0)	0
PR	2 (4)	0 (0)	2 (13)	0
CI	22 (48)	0 (0)	6 (32)	16 (70)
SD	20 (43)	4 (100)	10 (53)	6 (26)
PD	2 (4)	0 (0)	1 (5)	1 (4)

CHCR: clinicohematologic complete response; PR: partial response; NR: no response; PD: progressive disease; CR: complete response; CI: clinical improvement; SD: stable disease.

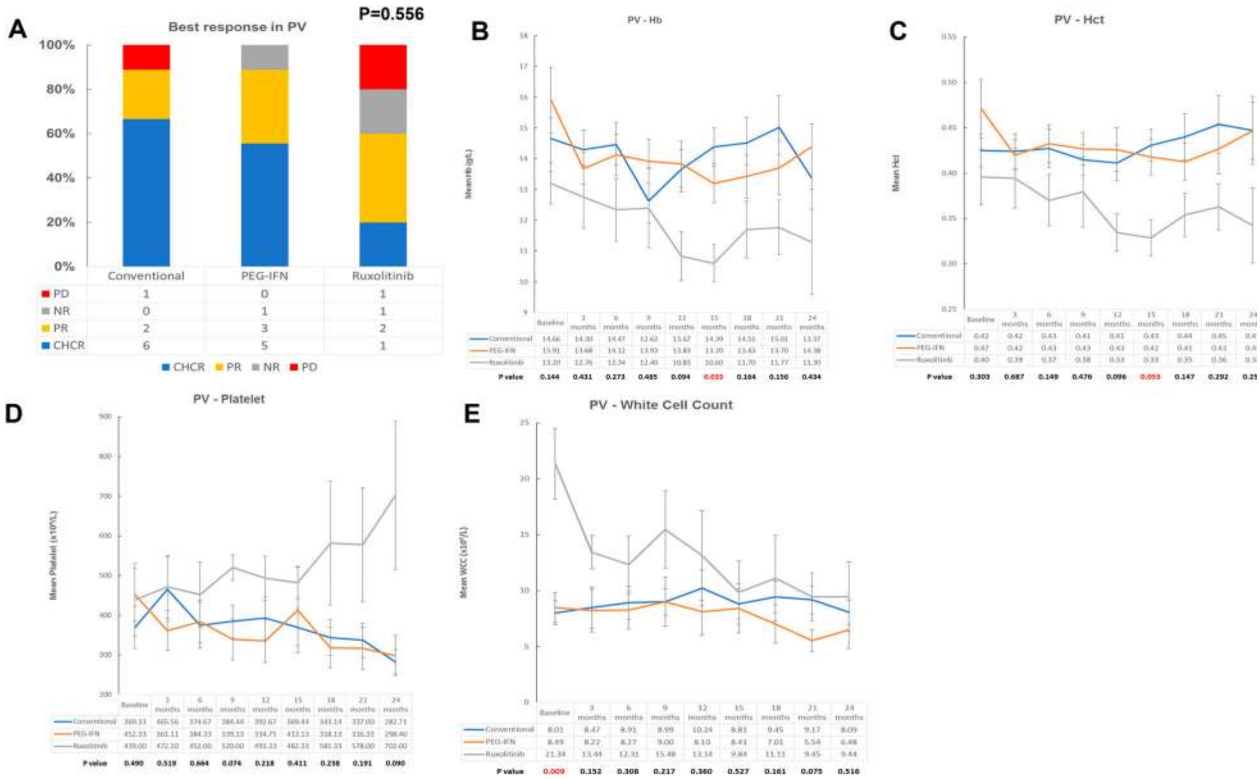

Figure 2. Hematological responses and changes in laboratory parameters in patients with polycythemia vera (PV). (A) Stacked bar chart showing best responses in patients with PV with different treatment. *P*-value denotes the overall differences in responses by χ^2 test. CHCR: clinicohematologic complete response; PR: partial response; NR: no response; PD: progressive disease. (B–E) Changes in hemoglobin (Hb), hematocrit (Hct), platelet count and white cell count during follow-up. *P*-value at each time point denotes the differences between the 3 treatment groups, compared with one-way analysis of covariance (ANCOVA), incorporating baseline values as a covariate to ensure that differences at different time points are unaffected by baseline inter-group variations.

cohort, DIPSS scores were low ($N = 4$, 9%), intermediate-1 ($N = 19$, 41%), intermediate-2 ($N = 22$, 48%) and high ($N = 1$, 2%); and the DIPSS-plus scores were low ($N = 3$, 7%), intermediate-1 ($N = 18$, 39%), intermediate-2 ($N = 20$, 44%) and high ($N = 5$, 11%). *JAK2*V617F, *CALR* and *MPL* mutations were present 33 (72%), 6 (13%) and 1 (2%) patients respectively (supplemental file 10). Other frequently mutated genes included *KMT2D* ($N = 18$, 39%), *ASXL1* ($N = 12$, 26%), *TET2* ($N = 11$, 24%), *NOTCH1* ($N = 11$, 24%), *GNAS* ($N = 10$, 22%), *KMT2B* ($N = 9$, 20%), *SETBP1* ($N = 8$, 17%), *CUX1* ($N = 7$, 15%) and *TP53* ($N = 6$, 13%) (supplemental file 10). VAF of mutated genes and co-occurring mutations were shown in supplemental files 10 and 11.

Treatment and outcome in MF. Amongst treatment groups, the gender, age, hemoglobin, hematocrit, platelet count, LDH, circulating blasts, splenomegaly, DIPSS scores, and DIPSS-plus scores were comparable. However, patients in the PEG-IFNα-2A group had significant lower leucocyte count ($P = 0.008$) (supplemental file 12). All patients were assessable for responses (Table 2, Figure 4). CR was not achieved in any cases. PR was observed in 2 patients (4%), whereas CI was seen in 22 patients (48%), with best responses achieved after a median of 3 (range: 3–9) months. There were no significant differences in the time to best responses between the 3 treatment groups ($P = 0.39$). Twenty patients (43%) achieved SD, and 2 patients developed disease progression (>50% increase in spleen size, PEG-IFNα-2A-treated; accelerated phase MF, ruxolitinib-treated). Ruxolitinib resulted in significantly superior CI ($P = 0.018$), and significantly lower hemoglobin and hematocrit from 6 to 18 months, with a gradual recovery to baseline levels beyond 18 months. Of the NGS panel, *JAK2*V617F was associated with superior responses (PR + CI) ($P = 0.04$) (supplemental file 7).

Responses in splenomegaly. To increase sample size, the whole MPN cohort was evaluated for spleen response. Pre-treatment spleen size was significantly larger in the ruxolitinib-treated group ($P < 0.001$). Despite this difference, patients treated with ruxolitinib had rapid and sustained spleen responses during the study (Figure 5(A)).

Responses in QOL. The mean MPN-SAF TSS for patients with PV, ET and MF were 19.8, 24.6 and 23.9 respectively ($P = 0.51$). The median total symptom scores were comparable for PV (16.5; range: 0–50), ET (25.5; range: 0–72) and MF (19; range: 0–74) (Figure 5(B)). Amongst symptoms, fatigue was the most serious in all MPN subtypes (supplemental file 13). ET patients had significantly higher scores for bone pain ($P = 0.047$), whereas MF patients had significantly more unintentional weight

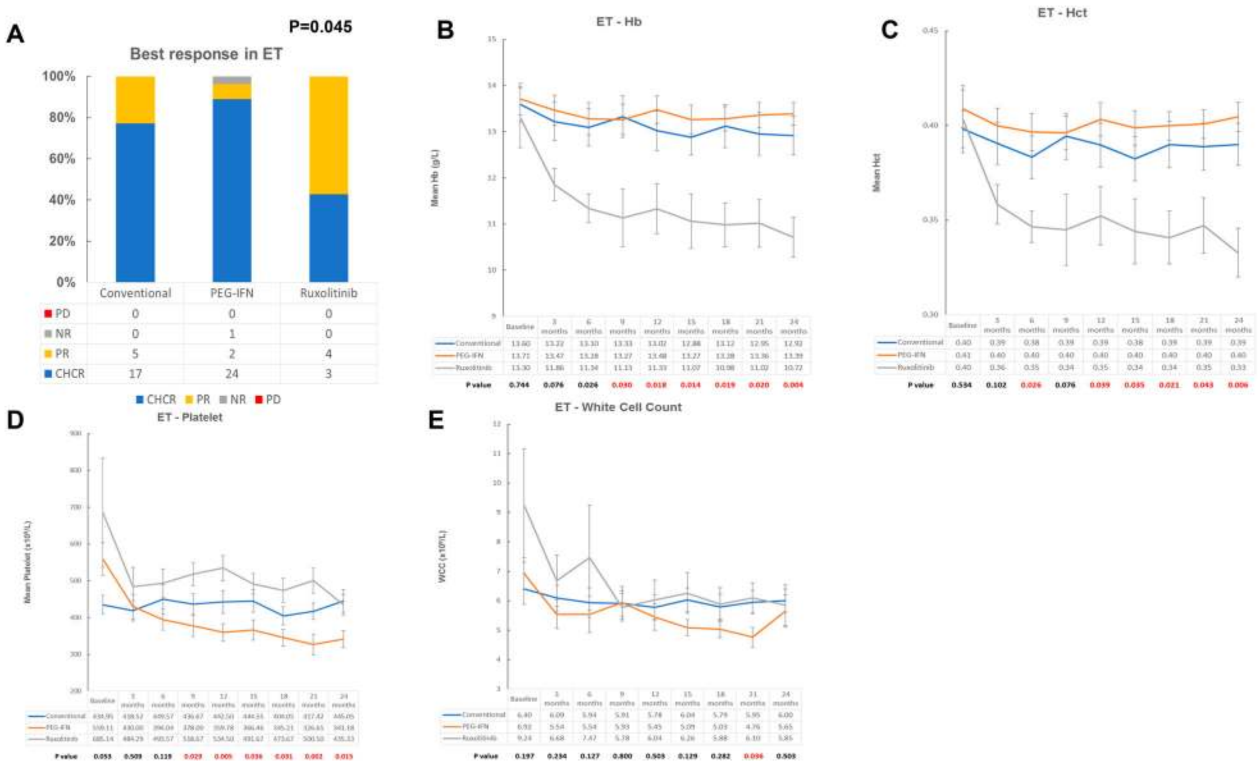

Figure 3. Hematological responses and changes in laboratory parameters in patients with essential thrombocythemia (ET). (A) Stacked bar chart showing the best responses in patients with ET with different treatment. *P*-value denotes the overall differences in responses by χ^2 test. CHCR: clinicohematologic complete response; PR: partial response; CI: clinical improvement; SD: stable disease; PD: progressive disease. (B–E) Changes in hemoglobin (Hb), hematocrit (Hct), platelet count and white cell count during follow-up. *P*-value at each time point denotes the differences between the 3 treatment groups compared using the one-way analysis of covariance (ANCOVA), incorporating baseline values as a covariate to ensure that differences at different time points are unaffected by baseline inter-group variations.

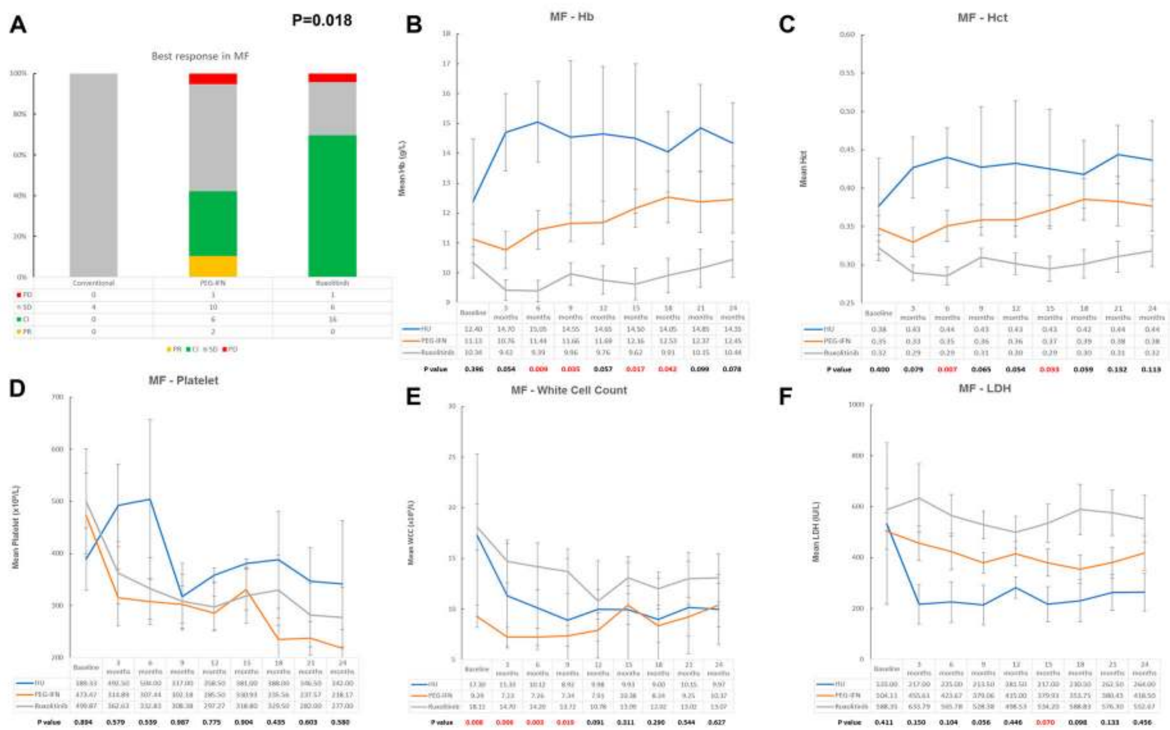

Figure 4. Hematological responses and changes in laboratory parameters in patients with myelofibrosis (MF). (A) Stacked bar chart showing the best responses in patients with MF with different treatment. *P*-value denotes the overall differences in responses by χ^2 test. PR: partial response; NR: no response; PD: progressive disease. (B–F) Changes in hemoglobin (Hb), hematocrit (Hct), platelet count, white cell count and lactate dehydrogenase (LDH) during follow-up. *P*-value at each time point denotes the differences between the 3 treatment groups compared using the one-way analysis of covariance (ANCOVA), incorporating baseline values as a covariate to ensure that differences at different time points are unaffected by baseline inter-group variations.

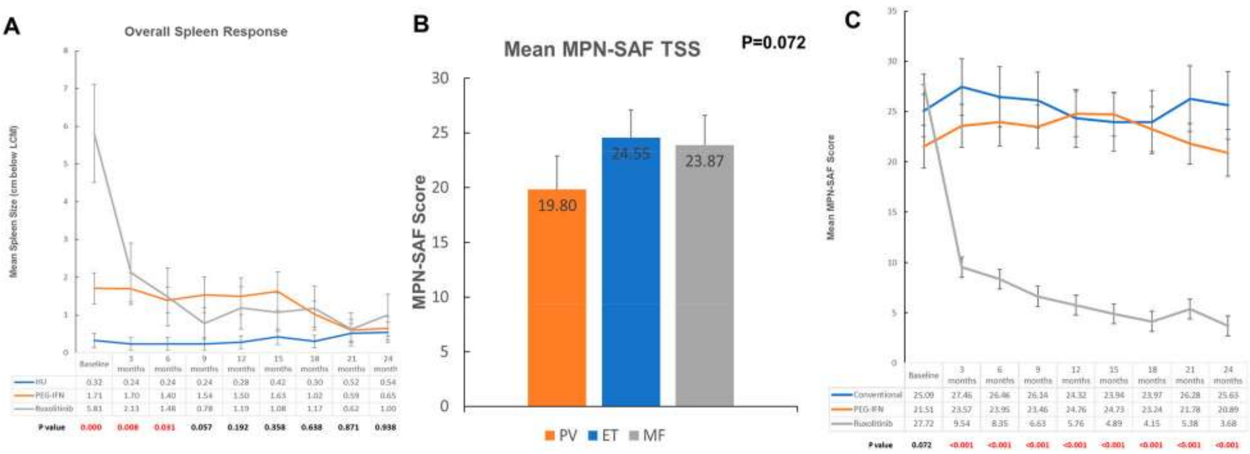

Figure 5. Changes of splenomegaly and quality-of-life in the whole cohort. (A) Responses in spleen size in patients with myeloproliferative neoplasms. *P*-value at each time point denotes the differences between the 3 treatment groups compared using the one-way analysis of covariance (ANCOVA), incorporating baseline values as a covariate to ensure that differences at different time points are unaffected by baseline inter-group variations. (B) Mean myeloproliferative neoplasm symptom assessment form total symptom score (MPN-SAF TSS) in patients with polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF). (C) Longitudinal changes in MPN-SAF TSS in 125 patients with myeloproliferative neoplasms. *P*-value at each time point denotes the differences between the 3 treatment groups compared using the one-way analysis of covariance (ANCOVA), incorporating baseline values as a covariate to ensure that differences at different time points are unaffected by baseline inter-group variations. LCM: left costal margin along Gardner's line.

loss ($P = 0.044$). Ruxolitinib resulted in significantly superior improvement in QOL as compared with conventional therapy and PEG-IFNα-2A ($P < 0.001$) (Figure 5(C)). Marked improvement in QOL in ruxolitinib-treated patients was seen within 3 months of therapy, and sustained throughout the study. The superiority of ruxolitinib over conventional therapy and PEG-IFNα-2A was observed across all symptom burden domains (supplemental file 14).

AEs. Grade 1–2 AEs were most frequent (hydroxyurea: 44%; PEG-IFNα-2A: 61%; ruxolitinib: 20%) (Table 3). Grade 3–4 AEs were infrequent and observed in patients treated with PEG-IFNα-2A (7%) and ruxolitinib (9%) but not hydroxyurea. The AEs were also

Table 3. Adverse events during the treatment of 125 patients with myeloproliferative neoplasms.

	Hydroxyurea ($N = 35$)		PEG-IFNα-2A ($N = 55$)		Ruxolitinib ($N = 35$)	
Grading of AEs	1–2	3–4	1–2	3–4	1–2	3–4
Total number of patients (%) with AEs[a]	15 (44)	0	34 (62)	4 (7)	7 (20)	3 (9)
Hematologic						
Anemia	1 (3)	0	4 (7)	2 (4)	7 (20)	0
Neutropenia	6 (17)	0	13 (24)	0	0	0
Thrombocytopenia	1 (3)	0	1 (2)	0	0	0
General						
Fluid retention	0	0	1 (2)	0	0	0
Dizziness	0	0	0	0	1 (3)	0
Weight gain	0	0	0	0	1 (3)	0
Rash	1 (3)	0	6 (11)	1 (2)	0	0
Alopecia	1 (3)	0	2 (4)	0	0	0
Musculoskeletal						
Fatigue	3 (9)	0	13 (24)	0	0	0
Myalgia	1 (3)	0	3 (5)	0	0	0
Gastrointestinal						
Anorexia	0	0	1 (2)	0	0	0
Mucositis	6 (17)	0	1 (2)	1 (2)	0	0
Diarrhea	0	0	2 (4)	0	0	0
Dyspepsia	0	0	1 (2)	0	0	0
Flatulence	0	0	0	0	1 (3)	0
Hepatotoxicity	3 (9)	0	13 (24)	0	2 (6)	0
Others						
Tuberculosis	0	0	0	0	0	2 (6)
Infections	0	0	0	0	0	1 (3)
Myasthenia gravis	0	0	0	1 (2)	0	0
Acute pericarditis	0	0	0	1 (2)	0	0
Thyroiditis	0	0	0	0	0	0
Depression	0	0	0	0	0	0
Death	0		0		1 (3)	

AEs: Adverse events.
[a]The same patient with ≥2 AEs were counted as one as a single patient may experience ≥2 AEs.

distinctive for different treatment groups. For hydroxyurea, AEs included mucositis (17%), neutropenia (17%), hepatitis (9%) and fatigue (9%). For PEG-IFNα-2A, besides neutropenia (24%) and anemia (11%), the other AEs could conceivably have an immunologic basis, including fatigue (24%), liver dysfunction (24%), rash (13%), pericarditis (2%) and myasthenia gravis (2%). Five patients (9%) discontinued PEG-IFNα-2A due to AEs (3 due to cytopenia and 2 due to autoimmune phenomena). For ruxolitinib, besides anemia (20%), the other AEs were infective. These included disseminated *Mycobacterium tuberculosis* infection (2 patients, 6%; occurring 6 and 9 months post-treatment) and *Mycobacterium avium complex* (MAC) lung infection (1 patient, 3%, with underlying bronchiectasis, occurring 9 months post-treatment); and virologic reactivation of HBV infection (detectable circulating HBV DNA) in 4 of 15 (27%) patients who had occult HBV infection (HBsAg-negative, anti-HBc-positive) at a median of 10.5 (range: 6.9–12.8) months post-treatment. The estimated incidences of HBV reactivation at 6 and 12 months were 8% and 31% (29). Three patients (9%) discontinued ruxolitinib due to AEs, all due to grade 3–4 infections.

Discussion

In this prospective cohort study, we showed that hydroxyurea, PEG-IFNα-2A and ruxolitinib were efficacious in MPN patients. For PV patients, ORRs were comparable for all three modalities. However, ruxolitinib did not effectively control platelet counts. For ET, practically all patients responded to treatment. PEG-IFNα-2A resulted in superior CHCR rates; whereas ruxolitinib led to significantly worse hemoglobin and inferior platelet control. For MF, CR could not be achieved in any patient. Ruxolitinib achieved the best CI. For the entire MPN cohort, reduction in splenomegaly was only observed in ruxolitinib-treated patients, which was durable throughout the study. Except *CREBBP* mutations in PV and *JAK2*V617F in MF, mutations in genes in the NGS panel did not impact on outcome.

These results show that other than ORR, other factors also affect the choice of treatment. In PV, hydroxyurea is recommended for high-risk patients [1]. Although a leukemogenic potential of hydroxyurea could not be established in uncontrolled studies, leukemic transformation actually increased with duration of treatment. Hence, hydroxyurea should be used cautiously in young patients. Ruxolitinib is approved for PV patients intolerant to hydroxyurea. However, for patients with concomitant thrombocythemia, ruxolitinib might not achieve optimal control. PEG-IFNα had been reported to achieve ORR of 70–77%, similar to our results. Interestingly, complete molecular response (undetectable *JAK2*V617F) could be achieved, with a median time to response at 24 months [4,6,11]. Therefore, for young PV patients requiring cytoreductive treatment, PEG-IFNα may be a preferred choice.

In ET, hydroxyurea effectively controls thrombocythemia and had been shown to prevent vascular and thrombotic complications. Its prolonged use in young patients is still restricted by concerns of leukemogenesis. In ET intolerant or resistant to hydroxyurea, ruxolitinib did not achieve superior clinicohematologic responses compared with other forms of second-line therapy [44,45]. It is noteworthy that ET treated with ruxolitinib had more significant and rapid reduction in symptom burden [44]. PEG-IFNα achieved CHCR in about three quarters of patients, similar to our results. Furthermore, molecular responses can be observed in approximately 41% and complete molecular response can be achieved in 5-10% of patients [4,46,47]. Hence, PEG-IFNα remains a preferred choice for young ET patients.

In intermediate-2 and high risk MF, the COMFORT-I and COMFORT-II studies have shown that ruxolitinib use is associated with significant clinical benefits in controlling splenomegaly, ameliorating disease-related symptoms, improving QOL and prolonging survivals, compared with placebo or best-available-therapy. In the COMFORT-I study, ≥35% reduction in spleen volume and ≥50% improvement in MPN-SAF was seen in 42% and 46% of patients respectively at 24 weeks [18]. In the COMFORT-II study, ≥35% reduction in spleen volume was seen in 28% of patients at 48 weeks [19]. The 5-year follow-up data from the COMFORT-I study also demonstrated prolonged median OS compared with placebo [48–50]. In the ROBUST trial, ruxolitinib resulted in ≥50% reduction in palpable spleen length and ≥50% reduction in MPN-SAF at 48 weeks respectively [51]. In the JUMP study, 61% of patients with intermediate-1 risk MF achieved ≥50% reduction in palpable spleen length [52]. Similarly, our study showed that ruxolitinib achieved clinical improvement in most patients, associated with rapid and sustained control of symptom burden and splenomegaly. Long-term use of ruxolitinib also resulted in ≥50% reduction in *JAK2*V617F allele burden [53]. Mutations in *ASXL1*, *EZH2*, or *IDH1/2*, or ≥3 mutations on a multigene panel, were associated with poor treatment responses and outcome following ruxolitinib [54,55]. In MF, PEG-IFNα has only been evaluated in small case series or retrospective studies [56,57]. Similar to our results, ORR (CR + PR + CI) was achieved in 50% of patients, and ≥50% reduction in spleen size in 40% of cases [56]. Responses were encouraging in early MF treated with PEG-IFNα, with control of leukocytosis and thrombocytosis seen in approximately 80% of patients, and spleen size reduction in 47% of cases [57]. Complete responses were however uncommon (<10%), and molecular responses were rarely reported. In overt MF with significant symptom burden and splenomegaly, ruxolitinib achieved the greatest benefit. The role PEG-IFNα in

MF remains to be defined, with benefits more probable in early MF [58].

In this study, distinct patterns of adverse events were seen in different treatment modalities. In patients treated with hydroxyurea, the main AEs were neutropenia and mucositis (17% each). This was similar to previous studies. Mucocutaneous ulceration, in particular, was observed in around 13–16% of patients who cannot tolerate hydroxyurea [59–61]. Cytopenia, hepatitis and immune-mediated AEs predominate in patients treated with PEG-IFNα. In our cohort, major AEs associated with PEG-IFNα were neutropenia, fatigue and transaminitis, mostly grade 1–2, which were similar to previously reported studies [4,11,46]. One patient developed myasthenia gravis. Thyroiditis or depression was not observed in our cohort. This is in contrast to recent studies in PV and ET reporting psychological complications and thyroid dysfunction in 10–40% and 10–25% respectively [11,46]. In our cohort, anemia and infective complications were the key AEs observed. Anemia was less severe in our cohort compared with published studies, with no patients requiring treatment discontinuation due to anemia. Grade 3–4 anemia was reported in 45% and 42% of patients with MF receiving ruxolitinib in the COMFORT-I and COMFORT-II studies [18,19]. We adopted a starting dose of 10 mg twice daily and a gradual dose-escalation by 10 mg every 4 weeks and a transfusion threshold of 7 g/dL. A dose-escalation approach may reduce the incidence of anemia, which may lead to drug discontinuation or dose reduction [62]. Thalidomide and erythropoietin stimulating agents were not used for the treatment of anemia during the study. In ruxolitinib-treated patients, tuberculosis occurred in 6% of patients in our study, in contrast to 1% reported in the COMFORT-II study [19]. This is likely due to the higher prevalence of tuberculosis in the Asian population. In addition, patients with occult HBV infection had estimated HBV DNA reactivation rates of 8% and 31% at 6 and 12 months [34]. This observation is unique to our population, due to a high seroprevalence of anti-HBc in East Asians [34]. Pre-emptive use of entecavir effectively prevented clinical hepatitis.

In a non-trial setting, our results showed that conventional therapy, PEG-INFα and ruxolitinib all induced responses in MPN. However, significantly better responses were only associated with PEG-IFNα and ruxolitinib in specific settings. Safety profiles were different for these modalities. Prospective comparative studies between these two modalities are needed in order to critically appraise their relative merits in different MPNs.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Rita Yim http://orcid.org/0000-0002-1754-1247
Paul Lee http://orcid.org/0000-0002-4149-0435
Jun Li http://orcid.org/0000-0001-7218-429X

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