Gender Determines Myeloproliferative Neoplasms Phenotype Independently of Age, Driver mutation and JAK2V617F burden

Theodoros Karantanos¹, Shruti Chaturvedi², Styliani Karanika³, Evan M. Braunstein², Linda Resar², Jerry L. Spivak², Alison R. Moliterno²

1. Division of Medical Oncology, Johns Hopkins Kimmel Cancer Center, Baltimore, MD
2. Division of Hematology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD
3. Department of Internal Medicine, Boston University Medical Center, Boston, MA

Abstract

INTRODUCTION: The prevalence of myeloproliferative neoplasms (MPN) is higher among females but males have overall worse outcomes. The aim of our study was to evaluate the impact of gender in presenting phenotype, disease progression, complications and mortality in a well-defined, prospective observational cohort.

PATIENTS AND METHODS: 630 individuals with ET, PV or PMF were enrolled in our observational cohort between 2005-2015. All individuals were genotyped for neutrophil JAK V617F variant allele frequency (VAF), and JAK2 V617F-negative individuals were studied for other JAK2 mutations, CALR or MPL mutations. Multivariable logistic regression was used to evaluate associations of gender, age and molecular characteristics with presenting phenotype.

RESULTS: The cohort comprised 630 individuals (384 females and 246 males). Males had a higher mean age at presentation (52.9 versus 48.8 years, P=0.002). Males were more likely to present with PMF (P <0.001), and this sex difference remained statistically significant across JAK2 V617F positive and negative groups, and across age groups (≤40 years, >40 and ≤60 years, and >60 years). Among the 185 patients who died during 2005-2015, males still presented more frequently with PMF (P=0.001), a difference that remained significant in both JAK2V617F-positive (P=0.023) and JAK2V617F-negative (P=0.018) subgroups. In a multivariable logistic regression model, male sex was significantly associated with PMF at presentation (P<0.001) after adjusting for age at diagnosis (P=0.4), neutrophil and CD34+ JAK2 V617F VAF (P=0.729 and P=0.064 respectively). Females had a higher rate of venous thromboembolism (15.7% vs. 6.9%, P<0.001) while males had higher rates of progression to AML (6.5% vs. 2.9%, P=0.028) and overall mortality (38.2% vs. 23.7% P<0.001).

CONCLUSIONS: Males with MPN present more frequently with PMF even when adjusting for age, and JAK2 VAF in neutrophils and CD34+ cells. Our transformation and survival data also suggest that males in our cohort appear to have worse outcomes compared to females. These striking sex-based differences in MPN presentation and outcomes demonstrate that male sex is associated with more aggressive disease biology independent of other factors, and further studies to dissect the molecular mechanisms are warranted.

Introduction

The chronic myeloproliferative neoplasms (MPN): essential thrombocythosis (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) share mutations of JAK2, MPL and CALR but vary widely with regards to sex distribution, age at diagnosis, disease progression, and survival. Males have overall worse clinical outcomes with decreased survival (1). However, the age and the molecular characteristics at diagnosis affect the presenting phenotype and influence the progression and outcomes (2). The aim of our study was to evaluate the impact of sex in the phenotype at diagnosis independently of age and JAK2 V617F burden and its effect on disease progression, complications and mortality rate.

Patients and Methods

630 individuals with ET, PV or PMF were enrolled in our observational cohort between 2005-2015. All individuals were genotyped for neutrophil JAK2 V617F VAF. All the JAK2 V617F negative patients were genotyped for other JAK2 mutations, CALR or MPL mutations. 121 individuals were genotyped for CD34+ cells JAK2 V617F VAF. The mean relative prevalence of the different phenotypes of MPN in males and females were compared using Fisher analysis. Univariate and multivariable logistic regression were used to evaluate associations of sex, age and molecular characteristics with presenting phenotype.

Results

Our cohort comprised 630 individuals (**Table 1**) with a total of 6819 patient-years and a median follow up of 9 (Q25-75% 6, 15) years.. The mean duration from initial diagnosis until enrollment was 7.2 years. Males had a higher age at presentation (52.9 versus 48.8 years, P=0.002). Females comprised the majority of the MPN cohort overall (F:M 1.56), in both the Caucasian (1.48) and, strikingly, in African-American MPN subsets (F:M 2.88). In contrast, females and males were similar in the Asian MPN subset (F:M 1.0).

Males were more likely to present with PMF compared to females (P<0.001). We did not identify any differences between females and males with regards to the driver mutation (JAK2 V617F, CALR, MPL, triple negative and other JAK2 mutations), presence of additional mutations or karyotypic abnormalities (Table 2). The prevalence of different phenotypes at presentation are presented in Figure 1.

Table 1: MPN Cohort Demographics

Variable	All patients	Females	Males	P
N	630	384	246	
Age at diagnosis (years), mean ± SD	50.38 ± 16.1	48.8 ± 16.2	52.9 ± 15.7	0.002
Race				
Caucasian	545 (86.5)	325 (84.6)	220 (89.4)	0.075
African American	62 (9.8)	46 (12.0)	16 (6.5)	0.048
Hispanic	3 (0.5)	3 (0.8)	0 (0.0)	
Asian	20 (3.2)	10 (2.6)	10 (4.1)	0.354

Table 2: Clinical and Molecular Features at MPN Initial Diagnosis

Variable	All patients (N=630)	Females (N=384)	Males (N=246)	P
Presenting characteristics				
Phenotype at diagnosis, n (%)				
ET	297 (47.1)	204 (53.1)	93 (37.8)	<0.001
PV	247 (39.2)	145 (37.8)	102 (41.5)	
PMF	86 (13.7)	35 (9.1)	51 (20.7)	
Genotype				
JAK2 +	489 (77.6)	294 (76.6)	195 (79.3)	0.237
CALR +	83 (13.2)	48 (12.5)	35 (14.2)	
MPL +	12 (1.9)	9 (2.3)	3 (1.2)	
Triple negative	32 (5.1)	25 (6.5)	7 (2.8)	
JAK2 – but others not done	14 (2.2)	8 (2.1)	6 (2.4)	
Additional mutations(N=102)				0.769
0	72 (70.6)	40 (69.0)	32 (72.7)	
1	17 (16.7)	11 (19.0)	6 (13.6)	
≥ 2	13 (12.7)	7 (12.1)	6 (13.6)	
Karyotype (N=279)				
Normal	178 (63.8)	107 (67.3)	71 (59.2)	0.296
1 lesion	48 (17.2)	23 (14.5)	25 (20.8)	
≥ 2 lesions	53 (19.0)	29 (18.2)	24 (20.0)

Figure 1. Males were more likely to present with PMF than ET and PV compared to females (P<0.001) and females were more likely to present with ET compared to males (P<0.001).

Next we stratified the patients at different age groups (Table 3 and figure 2). In the group of 40 years old or younger, males had higher prevalence of PMF (P=0.014). In the group of patients with age between 40 and 60 years, females had higher prevalence of ET compared to males (P=0.017). Among patients older than 60 years, females had higher prevalence of ET (P=0.011) and males had higher prevalence of PMF (P=0.021).

Table 3: Phenotypes at presentation at different age groups

Age group		Female	Male	P
≤ 40 years (N=182)	ET	83 (65.9)	38 (67.9)	0.052
	PV	38 (30.2)	11 (19.6)	
	PMF	5 (4.0)	7 (12.5)	
>40 years to ≤ 60years (N=273)	ET	85(51.5)	38 (35.2)	0.017
	PV	66 (40.0)	53 (49.1)	
	PMF	14 (8.5)	17 (15.7)	
> 60 years (N=175)	ET	36 (38.7)	17 (20.7)	0.011
	PV	41 (44.1)	38 (46.3)	
	PMF	16 (17.2)	27 (32.9)

Figure 2. Males have increased risk of presenting with more advanced disease and particularly PMF compared to males at all age groups.

Next, we stratified the patients based on their JAK2 V617F status and found that males with JAK2 V617F mutations have increased prevalence of PMF (P<0.001). In the JAK2 V617F negative group males have increased prevalence of PMF compared to females but the difference did not reach statistical significance (P=0.056) (Figure 3).

Figure 3. Males with JAK2V617F positive disease were more likely to present with PMF than ET and PV compared to females (P<0.001). Males with JAK2V617F negative disease have higher prevalence of PMF at presentation but the difference did not reach statistical significance (P=0.056).

Focusing on the 185 patients who died during the period 2005-2015, males have higher prevalence of PMF at presentation (P=<0.001), a difference that was statistically significant in both JAK2V617F-positive (P=0.023) and JAK2V617F-negative (P=0.018) subgroups (Figure 4).

Figure 4. Among the 185 patients who died during the period 2005-2015, males had higher prevalence of PMF at presentation (P<0.001) in both JAK2 V617F-positive (P=0.023) and JAK2 V617F-negative group (P=0.018).

Next, we focused on 275 patients with JAK2V617F VAF in both neutrophils and CD34+ cells within 5 years from diagnosis and performed logistic regression analysis. Male sex was associated PMF at presentation after adjusting for age at diagnosis (P=0.4), neutrophil and CD34+ JAK2 V617F VAF (P=0.729 and P=0.064 respectively). Finally, we found that males have increased risk of AML transformation (P=0.028) and death from any cause (P<0.001) while females have increased risk of venous and arterial thrombosis (P=0.001) (Table 4).

Table 4: Outcomes of females and males with MPN

Variable	All patients (N=630)	Females (N=384)	Males (N=246)	P
Outcomes				
DVT or visceral thrombosis (N=629)	77 (12.2)	60 (15.7)	17 (6.9)	0.001
CVA or MI (N=628)	69 (11.0)	39 (10.2)	30 (12.2)	0.420
Transformation to MF (N=544)	111 (20.4)	64 (18.3)	47 (24.1)	
Transformation to AML	27 (4.3)	11 (2.9)	16 (6.5)	0.028
Death	185 (29.4)	91(23.7)	94 (38.2)	<0.001

Conclusions

- Males with MPN have higher prevalence of PMF and females higher prevalence of ET at presentation.
- When stratified per age, males younger than 40 and older than 60 years have higher prevalence of PMF at presentation and females older than 40 years have higher prevalence of ET at presentation.
- When stratified per JAK2 V617F status, males with JAK2 V617F-positive disease have higher prevalence of PMF at presentation. The difference did not reach statistical significance in the JAK2V617F-negative group.
- Male sex is associated with PMF at presentation independently of age at diagnosis and JAK2 V617F VAF in neutrophils and CD34+ cells.
- Males have higher risk of AML transformation and death from all causes compared to females.
- These data suggest that male sex is associated with more aggressive disease biology independent of other factors, and further studies to dissect the molecular mechanisms are warranted.

References

1. Tefferi et al. Gender and survival in essential thrombocythemia: A two-center study of 1,494 patients. Am J Hematol. 2017 Nov;92(11):1193-1197
2. Rozovski et al. An accurate, simple prognostic model consisting of age, JAK2, CALR, and MPL mutation status for patients with primary myelofibrosis. Haematologica. 2017 Jan;102(1):79-84