

Effects of Mutational Combinations on Philadelphia-Negative Myeloproliferative Neoplasms

Dear Editor,

Philadelphia-negative myeloproliferative neoplasms (MPNs) were first described 65 years ago. Yet, the molecular features of the disease have become of interest since 2005 following the identification of the JAK2V617F mutation.¹ Between 90% and 98% of patients with polycythemia vera and about 50% of patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF) harbor the JAK2V617F mutation.² In recent years, additional genetic factors such as the mutations of IDH1/2, TET2, EZH2, ASXL1, and CALR have been identified in Ph-negative MPNs.³ However, the significance of mutational combinations on Ph-negative MPNs remains unknown.

We have previously demonstrated that in PMF, ASXL1 and IDH mutations were associated with shorter survival and leukemic transformation, respectively.^{4,5} Yet in patients with ET, the aforementioned mutations did not show an effect on overall survival.^{4,5} Patients with ET carrying the ASXL1-mutation showed a trend toward an increase in the incidence of cerebrovascular events.⁴ Recently, we reported that both ASXL1 and IDH mutations showed a higher prevalence of bleeding complications in patients with PMF.^{4,5} In our previous study, no association was detected between overall survival and mutational status and allele burden of JAK2V617F in ET and PMF.⁴ Patients with PMF showed a higher prevalence of the JAK2V617F mutation than those with ET (75.3% and 59.8%, respectively; $P=0.028$) (table 1).⁶ Patients with PMF exhibited a higher frequency for ASXL1 mutations (exon 12) (24.7%) than those with ET (8.4%) ($P=0.005$) (table 1).⁴ With respect to the prevalence of IDH mutation (IDH1 or IDH2), patients with ET and PMF showed no significant difference (1.9% and 6.5%, respectively; $P=0.131$) (table 1).⁵ We had previously shown that 73.6% (14 in 19) of patients with ASXL1-mutated PMF carried the JAK2V617F mutation and 14 of 77 patients with PMF (18.2%) carried simultaneously, ASXL1 and JAK2V617F mutations.⁴ Furthermore, 66.6% (6 in 9) of patients with ASXL1-mutated ET carried the JAK2V617F mutation.⁴ Of 107 patients with ET, 6 (5.6%) simultaneously expressed ASXL1 and JAK2V617F mutations.⁴ Also, 60% (3 in 5) of patients with IDH-mutated PMF harbored JAK2V617F, whereas 50% (1 in 2) of patients with IDH-mutated ET harbored JAK2V617F.⁵ Patients with PMF demonstrated a significantly higher frequency for combined JAK2V617F and ASXL1 mutations than patients with ET (18.2% and 5.6%, respectively; $P=0.014$) (table 1).⁴ With regard to the prevalence of combined JAK2V617F and IDH mutations, patients with ET and PMF showed no significant difference (0.9% and 3.9%, respectively; $P=0.31$) (table 1).⁵ Among patients with ET, combined ASXL1 and JAK2V617F mutations showed no correlation with leukocyte count, platelet count, lactate dehydrogenase (LDH) level, spleen size, bleeding complications, total thrombotic events, arterial thrombosis, and venous thrombosis ($r<0.2$).⁴ A mild positive correlation between bleeding events and combined ASXL1 and JAK2V617F mutations was demonstrated in patients with PMF ($r=0.363$).⁴ No correlations were detected between Htc level, leukocyte count, platelet count, LDH level, mean spleen size, total thrombotic events, arterial thrombosis, venous thrombosis and combined ASXL1 and JAK2V617F mutations ($r<0.2$).⁴ Furthermore, in patients with PMF, the presence of combined JAK2V617F and IDH mutations did not correlate with Htc level, leukocyte count, platelet count, LDH level, bleeding complications, total thrombotic events, arterial thrombosis, venous thrombosis, and death ($r<0.2$).⁵ In the present study, we analyzed the frequency and effect of the mutational combinations of ASXL1 and IDH in 77 patients with PMF and found that 15.7% (3 in 19) of the patients with ASXL1-mutated PMF carried IDH mutations. The 6 patients with ET carrying ASXL1 mutations did not harbor concurrent IDH mutations. There was a trend toward a higher prevalence of combined ASXL1 and IDH mutations in PMF compared to ET (3.9% and 0, respectively; $P=0.072$) (table 1). In the patients with PMF, we observed a weak positive correlation between bleeding complications and combined ASXL1 and IDH mutations ($r=0.24$). In the patients with PMF, no correlations were found between Htc level, leukocyte count, platelet count, LDH level, mean spleen size, total thrombotic events, arterial thrombosis, venous thrombosis, and combined ASXL1 and IDH mutations ($r<0.2$).

Our data indicated that in the patients with PMF, combined ASXL1 and JAK2V617F mutations and the co-presence of ASXL1 and IDH mutations had a significant effect on bleeding complications. We aim

Table 1: Clinical and laboratory features of the patients with ET and PMF

	n (%)			P value
	ET	PMF	Total cohort	
Number of patients	107	77	184	-
JAK2V617F mutation	64 (59.8%)	58 (75.3%)	122 (66.3%)	0.028
ASXL1 mutation	9 (8.4%)	19 (24.7%)	28 (15.2%)	0.005
IDH mutation (IDH1 or IDH2)	2 (1.9%)	5 (6.5%)	7 (3.8%)	0.131
Combined JAK2 and ASXL1 mutation	6 (5.6%)	14 (18.2%)	20 (10.9%)	0.014
Combined JAK2 and IDH mutation	1 (0.9%)	3 (3.9%)	4 (2.2%)	0.31
Combined ASXL1 and IDH mutation	0	3 (3.9%)	3 (1.6%)	0.072

ET: Essential thrombocythemia; PMF: Primary myelofibrosis

to search for mutational combinations in a larger group of Ph-negative MPNs to investigate their effect on the disease course and complications.

Conflict of Interest: None declared.

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