Concurrent driver mutations in MPN

Clinical and molecular characteristics of a series of 11 patients

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Patient characteristics

Patient	Age ^a	Gender	MPN type	Driver Mutations	Interval between diagnoses	Symptoms ^b	Clinical observation ^b
1	41	Male	ET→CML	JAK2 V617F/ BCR-ABL1 (p210)	13 years	None	Normal
2	64	Male	PMF→CML	JAK2 V617F/ BCR-ABL1 (p210)	3 years	Fever & weight loss/Abdominal discomfort	HSM
3	81	Male	ET + CML	JAK2 V617F/ BCR-ABL1 (p210)	0 year	Weight loss	Normal
4	78	Male	CML→ PPV-MF	JAK2 V617F/ BCR-ABL1 (p190)	2 years	Night sweats/ Weight loss	Splenomegaly
5	27	Female	PV→CML→ PPV-MF	JAK2 V617F/ BCR-ABL1 (p210)	5/8 years	None/Abdominal discomfort	Normal/HSM
6	60	Female	MDS/MPN-RS-T→CML	JAK2 V617F/ BCR-ABL1 (p210)	1 year	Fatigue/abdominal discomfort	HSM
7	46	Female	ET→post-ET MF→ CML	CALR type 2/ BCR-ABL1 (p210)	16/18 years	None/Fatigue/abdominal pain	Normal/HSM
8	73	Male	ET + CML	JAK2 V617F/ BCR-ABL1 (p210)	0 year	na	na
9	74	Female	ET	JAK2 V617F/ MPL W515R		Headache	Normal
10	71	Female	ET + CML	JAK2 V617F/ BCR-ABL1 (p210)	0 year	Fatigue	Normal
11	75	Male	PMF	JAK2 V617F/ CALR type 1		None	Splenomegaly

a: at diagnosis first MPN (years). b: at diagnosis (first/second MPN) Abbreviations: MPN: myeloproliferative neoplasm, ET: essential thrombocytosis, PV: polycythemia vera, PMF: primary myelofibrosis, PPV-MF: post-polycythemia vera myelofibrosis CML: chronic myeloid leukemia. MDS/MPN-RS-T: myelodysplastic/MPN overlap syndrome with ring sideroblasts and thrombocytosis. HSM: hepatosplenomegaly. na: not available.

Introduction

Myeloproliferative neoplasms (MPN) are categorized in different entities, which are distinct in both clinical and molecular presentation. Because of overlapping features, the diagnosis can be challenging. According to the WHO diagnostic criteria, MPN subtypes and their driver mutations are mutually exclusive. Yet, in the last few years, rare cases of coexisting MPN have been reported. Little is known about the clinical, biological and molecular characteristics of these patients and the interaction of the neoplastic clones.

Materials and Methods

We retrospectively studied 11 MPN patients with coexisting driver mutations:

- JAK2 V617F + BCR-ABL1: n=8
- CALR type 2 (p.K385Nfs*47) + BCR-ABL1: n=1
- JAK2 V617F + MPL W515: n=1
- JAK2 V617F + CALR type 1 (p.Leu367Thrfs*46): n=1

To assess possible associated molecular aberrations, we also analysed DNA of six patients using Next Generation Sequencing (NGS). To see the NGS results, scan the QR-code above.

Results

By NGS, additional somatic mutations were detected in 5 out of 6 (83%) patients (3, 5, 7, 9, 11) affecting 4 different genes, confirming the heterogeneity of this study cohort. Two of them (9, 11) presented with a CUX1 mutation. Interestingly, these cases corresponded to the only non-CML patients in the present series. In four CML patients (1, 2, 3, 7), decreasing BCR-ABL1 transcript levels and increasing JAK2 V617F/CALR allele burden under Tyrosine Kinase Inhibitor (TKI) were observed. This suggests that the coexistence of driver mutations likely originates from two different clones growing independently. Furthermore, suboptimal response to TKI was observed with a higher frequency (4/8 patients: 1, 3, 4, 6) than reported in conventional series of CML and the overall tolerance of treatment with hydroxyurea and/or imatinib in our series was poor.

Follow-up of BCR-ABL1 transcript, JAK2 and CALR allele burden after start of imatinib

Follow-up of the BCR-ABL1 transcript and JAK2 allele burden after start of imatinib in patients 1, 2 and 3 and follow-up of the BCR-ABL1 transcript and CALR allele burden in patient 7. The increase of JAK2/CALR allele burden following eradication of the BCR-ABL1 transcript supports the hypothesis of two neoplasms originating from different clones growing independently. PB: peripheral blood cells.

Conclusion

Given that NGS is increasingly used in clinical laboratory practice, it is very likely that more cases will be identified in the coming years. Whether these patients are more likely to respond suboptimally to TKI, and are more susceptible to therapy-related toxicities, remains to be investigated in larger studies.