ORIGINAL ARTICLE

Profile of Philadelphia Chromosome Negative (Ph−) Myeloproliferative Neoplasm with Special Emphasis on Vascular Thrombotic Events and the Response to Cytoreductive Therapy in Polycythemia Vera and Essential Thrombocythemia Patients: A Single Center Study from Kerala

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Abstract

Introduction: Thrombotic events are a major morbidity among Philadelphia chromosome-negative myeloproliferative neoplasm (Ph-MPN) patients. There is a lack of data from Kerala regarding the profile of Ph-MPN and the prevalence of thrombosis among these patients.

Aims: To study the clinical profile, driver mutations, incidence of thrombotic events among Ph-MPN patients, and the response to hydroxyurea therapy.

Methods: We reviewed the medical records of 84 Ph-MPN patients who were on follow-up from April 2019 to June 2023 in a tertiary care hospital in Kerala.

Results: There were 48 polycythemia vera (PV), 16 essential thrombocythemia (ET), 14 primary myelofibrosis (PMF), and six unclassifiable MPN (MPN-u) patients. The incidence of Janus kinase 2 (JAK2) mutation was 96, 62.5, and 79% among PV, ET, and PMF patients, respectively. The incidence of calreticulin (CALR) mutation was 37.5 and 21% among ET and PMF patients, respectively. The incidence of thrombotic events was 23/48 (48%), 7/16 (43.5%), and 6/14 (42.8%) among PV, ET, and PMF patients, respectively. All ET and PMF patients with thrombotic events were JAK2V617F-mutated. Eighty-seven percent of the evaluable patients on hydroxyurea for PV achieved freedom from therapeutic phlebotomies. ET patients who were on hydroxyurea achieved a median platelet count of 4.3 lakhs/μL (3.16–6.08).

Conclusion: There is a higher incidence of thrombosis among Ph-MPN patients from Kerala, which needs to be ascertained in a population-based study. JAK2V617F mutation is the major determinant of thrombotic episodes in ET and PMF. Hydroxyurea is an effective cytoreductive therapy in PV and ET.

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Introduction

Philadelphia chromosome-negative myeloproliferative neoplasm (Ph-MPN) is a heterogeneous group of clonal hematopoietic stem cell disorders that are classified into polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic neutrophilic leukemia (CNL), mastocytosis, and myeloproliferative neoplasm-unclassifiable (MPN-u).[1] The diagnosis of Ph-MPNs typically involves a combination of clinical evaluation, peripheral blood counts, bone marrow examination, and molecular testing to identify specific mutations. The identifiable driver mutations in MPN are Janus kinase 2 (JAK2), calreticulin (CALR), and thrombopoietin receptor/myeloproliferative leukemia (MPL) mutations.[2] Major complications include thrombotic events such as stroke, myocardial infarction, and venous thrombosis. PV and ET can progress to secondary myelofibrosis and, rarely, to leukemia. Transformation to acute leukemia is relatively more common with PMF in comparison to other Ph-MPNs. Management of Ph-MPN mainly aims to control disease symptoms, reduce the risk of thrombotic or hemorrhagic complications, and tackle disease-related complications such as secondary myelofibrosis or transformation to leukemia. Treatment options include therapeutic phlebotomy, cytoreductive therapy, and/or targeted agents such as JAK inhibitors. Patients diagnosed with PV, ET, or primary/secondary myelofibrosis have an increased risk of mortality when compared with the general population.[3]

Hydroxyurea has been the conventional first-line treatment for patients with myeloproliferative neoplasms (MPNs) requiring cytoreductive therapy.[4] In PV, hydroxyurea is used primarily to suppress exaggerated hematopoiesis, thereby reducing the risk of thrombotic events associated with increased blood viscosity. In ET, hydroxyurea helps to mitigate the elevated platelet count by inhibiting megakaryocytic proliferation, thereby reducing the risk of thrombotic events such as stroke or myocardial infarction. Treatment with hydroxyurea requires regular monitoring for potential side effects, including myelosuppression, nonhealing leg ulcers, and gastrointestinal disturbances. An additional concern with hydroxyurea is the risk of secondary malignancies, such as leukemia and skin carcinoma, necessitating careful consideration of its benefits and risks.

There is a lack of data from Kerala regarding the clinical profile, incidence of thrombotic events, prevalence of driver mutations, and response to therapy among MPN patients.

Methods

This was a single-center, retrospective observational study.

We analyzed the medical records of Ph-MPN patients above 18 years of age who were on follow-up from April 2019 to June 2023 in a tertiary care hospital in Kerala, South India. The procedures followed in the study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as

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revised in 2013. The diagnosis of Ph-MPN was made according to the revised 2016 World Health Organization (WHO) classification. The main objectives were to evaluate the clinical characteristics, laboratory parameters, driver mutations (JAK2 V617F, JAK2 exon 12, CALR, and MPL mutations), therapy given, and response to therapy, especially hydroxyurea. Thrombotic events were analyzed in each subtype of Ph-MPN. Thromboembolic complications related to MPN were defined as thrombotic events that occurred up to 2 years before the MPN diagnosis or afterward. The occurrence of a thromboembolic event was recorded as the date of imaging when the event was objectively confirmed. Patients were categorized as high risk if they were above 60 years of age or had a history of a thrombotic event.

Categorical variables were represented by frequencies in numbers and rates in percentages. Continuous variables were expressed as median values and ranges.

Results

A total of 84 patients were diagnosed with Ph-MPN. Table 1 depicts their baseline characteristics. The median age was 61 years (21–85). Fifty-three patients were men (63%) and 31 were women (37%). Of the 84 patients, 48 had PV (including four with post-PV myelofibrosis), 16 had ET, 14 had PMF, and six had MPN-u.

Among the PV group, the median age of the patients was 59.5 years (21–76), with 36 (75%) men and 12 (25%) women. Forty-five (94%) PV patients harbored the JAK2 V617F mutation, 1/48 (2%) had a JAK2 exon 12 mutation, one was negative for both mutations, and in one patient, mutations were not examined (Fig. 1). Of these, 34 (71%) patients belonged to the high-risk (HR) group and 14 (29%) patients belonged to the low-risk (LR) group. Thrombotic events at or before diagnosis were reported in 23/48 (48%) patients. Thrombotic events included cerebrovascular accident (CVA) in 12 patients, transient ischemic attack (TIA) in two patients, coronary artery disease (CAD) in five patients, deep venous thrombosis (DVT) of the lower limbs in one patient, pulmonary thromboembolism (PTE) in one patient, and digital gangrene in one patient. Portal vein and mesenteric vein thrombosis occurred simultaneously in one patient. The median hemoglobin (Hb) level was 18 gm/dL (14–22.7), the median hematocrit was 55.9% (42.5–75.9), the median white blood cell (WBC) count was 11,590/µL (5,130–34,200), and the median platelet count was 4.34 lakhs/µL (1.2–10). One patient had covert PV, that is, blood counts were normal but JAK2 V617F positivity was detected during the evaluation of portal vein thrombosis (PVT). The median follow-up was 14.5 months. Low-risk patients were treated with low-dose aspirin and therapeutic phlebotomy to keep packed cell volume (PCV) <45%. Hydroxyurea was added to the above regimen for HR patients. Of the 23 evaluable HR patients on hydroxyurea, 20 (87%) were free from therapeutic phlebotomies by 3 months of therapy. None of the patients developed a new thrombotic event during follow-up. One patient with post-PV myelofibrosis (PV-MF) progressed to acute myeloid leukemia.

The ET group had a median age of 57.5 years (22–73), with four men (25%) and 12 women (75%). Ten patients were JAK2 V617F-positive, and six patients had a CALR mutation (Fig. 2). A total of 10/16

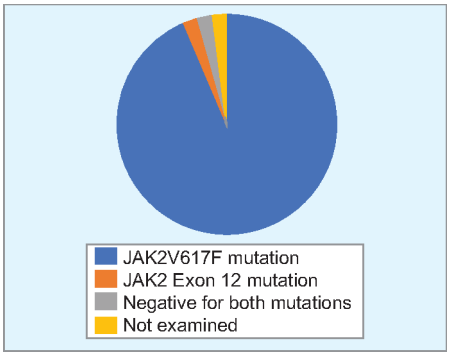

Fig. 1: Prevalence of driver mutations in PV

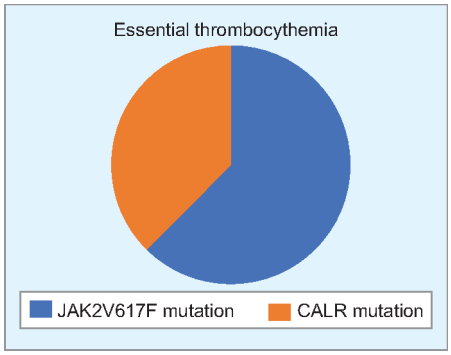

Fig. 2: Prevalence of driver mutations in ET

Table 1: Baseline characteristics of MPN patients

	MPN (n = 84)	*PV (n = 48)*	*ET (n = 16)*	*PMF (n = 14)*	*MPNu (n = 6)*
Age (years)	61 (21–85)	59.5 (21–76)	57.5 (22–73)	68 (50–78)	80.5 (53–85)
Gender	Male 53 (63%) Female 31 (37%)	Male 36 (75%) Female 12 (25%)	Male 4 (25%) Female 12 (75%)	Male 9 (64%) Female 5 (36%)	Male 4 (67%) Female 2 (33%)
Hb (gm/dL)	15.4 (6.5–22.7)	18 (14–22.7)	13 (9.9–16.3)	10.8 (6.5–16.9)	11.1 (10.5–14.9)
WBC (cells/µL)	11,245 (3,900–96,600)	11,590 (5,130–34,200)	8,335 (6,000–17,310)	12,200 (3,900–72,260)	29,055 (16,000–96,600)
Platelets (lakhs/µL)	4.88 (1.1–21.11)	4.34 (1.2–10)	8.84 (4.96–21.11)	4.15 (1.1–12.7)	5.04 (1.9–13.7)
Hematocrit (%)	47 (20.2–75.9)	55.9 (42.5–75.9)	39.6 (29.1–50.8)	34.35 (20.2–53.6)	34.95 (33.4–51.9)
Mutations					
JAK2	69 (82%)	46 (96%)	10 (62.5%)	11 (79%)	2 (33.3%)
CALR	9 (11%)	0	6 (37.5%)	3 (21%)	0
MPL	0	0	0	0	0
Triple neg	4 (5%)	1 (2%)	0	0	3 (50%)
Not done	2 (2%)	1 (2%)	0	0	1 (16.7%)
Thrombotic events	37 (44%)	23 (48%)	7 (44%)	6 (43%)	4 (67%)
Vasomotor events	17 (20%)	13 (27%)	1 (6%)	3 (21%)	0
Bleeding events	4 (5%)	3 (6%)	0	0	1 (17%)
Aquagenic pruritus	7 (8%)	6 (12.5%)	0	1 (7%)	0

CALR, calreticulin; ET, essential thrombocythemia; JAK2, Janus kinase 2; MPL, myeloproliferative leukemia virus oncogene; MPN, myeloproliferative neoplasm; MPN-u, myeloproliferative neoplasm, unclassifiable; PMF, primary myelofibrosis; PV, polycythemia vera; WBC, white blood cell

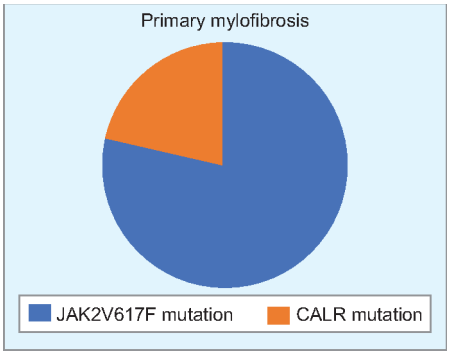

Fig. 3: Prevalence of driver mutations in PMF

(62.5%) patients belonged to the HR group. Seven patients (43.75%) had thrombotic events, which included five CVAs, one case of digital gangrene, and one patient with a combination of PVT and abdominal aortic thrombus with renal infarction. All patients with thrombotic events were JAK2 V617F-positive. The median platelet count at diagnosis was 8.84 lakhs/µL (4.96–21.11). The median follow-up was 9 months. ET patients were treated with antiplatelet agents, and hydroxyurea was added for HR patients. The median platelet count at the last follow-up for patients on hydroxyurea was 4.3 lakhs/µL (3.16–6.08).

The PMF group had a median age of 68 years (50–78), with nine men (64.7%) and five women (35.7%). Eleven of the 14 patients had a JAK2 V617F mutation, and three had a CALR mutation (Fig. 3). Five patients were in the prefibrotic phase. Eleven PMF patients had anemia, eight had leukocytosis, six had thrombocytosis, and one had thrombocytopenia at presentation. Six patients (42.8%) had thrombotic events, and all of them were JAK2 V617F-positive. There were two CAD events, three cases of peripheral arterial disease (one patient had a combination of CAD and peripheral arterial disease), one DVT of the lower limbs, and one PVT.

Discussion

In this observational study of Ph-MPN cases, driver mutations were assessed in all but two cases (one of which was PV and the other MPN-u). Ninety-six percent of our PV patients had driver mutations, with JAK2 V617F in 94% and JAK2 exon 12 mutation in 2%. In a study by Tefferi et al., 98% of PV patients had a driver mutation in the JAK2 gene.[5] The remaining patients can have noncanonical mutations in the pseudokinase domain of the JAK2 gene in exons 12–15.[6] We did not check for noncanonical mutations in the JAK2 gene, as sequencing for these alterations was not easily available. Also, we tested for driver mutations by real-time polymerase chain reaction (RT-PCR) techniques and not by deep sequencing. Deep-sequencing techniques may have identified cases in which the driver mutation allele burden was low. A meta-analysis of 29 studies, which included 13,436 MPN patients from Europe, North America, Asia, and Australia, reported that the pooled prevalence of arterial or venous thrombotic events at the diagnosis of MPN was 20% [95% confidence interval (CI), 16.6–23.8%], and the pooled prevalence in PV patients was 28.6% (95% CI, 22.0–36.3%).[7] Contrary to this meta-analysis and another study from India,[8] thrombotic events were more frequent in our study, with 44% of the total Ph-MPN cohort and approximately half of our PV patients affected. Whether this higher incidence of thrombosis in MPN patients in Kerala (a small state in southern India) reflects the higher prevalence of vascular disorders secondary to the high burden of diabetes and hypertension in Kerala or a unique feature of MPN in this locality needs to be ascertained in larger population studies. Hydroxyurea was well tolerated and very effective in controlling the red blood cell (RBC) mass in our HR-PV patients; 87% of the evaluable patients did not require further therapeutic phlebotomy, and none developed a new thrombotic event while on hydroxyurea.

In the ET group, JAK2 V617F mutation was found in 63% of patients, and the remainder were CALR mutation-positive. The incidence of JAK2 V617F mutation in our ET group concurs with previous reports.[9,10] We did not find any MPL-mutated ET cases. Previous studies reported that ET patients with JAK2 V617F mutation have a higher risk of thrombotic events than CALR- or MPL-mutated patients.[11,12] In our cohort, 44% of ET patients had major thrombotic events, and all of them were positive for JAK2 V617F mutation. This incidence of thrombotic events is higher compared to a previous Mayo Clinic study, in which 22% of patients had a thrombotic event.[13] There is no correlation between platelet count per se and the incidence of thrombosis in ET. However, it is a known fact that good control of thrombocytosis is essential to prevent further thrombotic events in ET. HR ET patients in our study who were treated with hydroxyurea achieved good control of thrombocytosis, as evidenced by a median platelet count of 4.3 lakhs/µL. Resistance to hydroxyurea leads to an increased risk of transformation to myelofibrosis (MF) and acute myeloid leukemia (AML).[14,15] All our patients tolerated hydroxyurea well and did not develop resistance during the follow-up period, and there were no new thrombotic events.

Among the PMF cohort in this study, JAK2 V617F and CALR mutations were found in 79 and 21% of patients, respectively. The incidence of JAK2 V617F mutation in our PMF group is higher compared to previous reports.[16] In this small group of PMF patients, none had MPL mutations. As was the case with ET, all PMF patients who had thrombotic events were JAK2 V617F-mutated. This concurs with the previously reported higher frequency of thrombotic events in JAK2-mutated PMF.[17,18] As with our other two Ph-MPN groups, the PMF cohort also had a higher incidence of thrombotic events (43%) compared with the previously reported 24% from an East Asian cohort.[19]

As our HR-PV patients had an excellent response to hydroxyurea, ruxolitinib was not required in our PV cohort. One patient with post-PV MF was started on ruxolitinib but rapidly progressed to AML. None of the PMF patients were treated with ruxolitinib, primarily because of the high cost of the drug, which was beyond their means. A second malignancy was seen in only one patient who had PV, which progressed to MF after 18 years and later to AML. The low rate of second malignancy in patients on hydroxyurea concurs with the previous analysis from the New Haven group of a large cohort of 2,683 MPN patients on hydroxyurea.[20]

To summarize, thrombotic events were seen in 48, 44, and 43% of our PV, ET, and PMF cohorts, respectively. This higher incidence of thrombosis, compared to previous studies, needs to be studied prospectively in population-based research. Consistent with previous reports, JAK2 V617F mutation remains a major determinant of thrombotic episodes in ET and PMF patients. Hydroxyurea is an efficient cytoreductive therapy in PV and ET, and none of our patients developed further thrombotic events after initiating therapy.

Our data reveal the real-life characteristics of MPN in South India. This will help research initiatives in this field, the fair allocation of limited healthcare resources, the understanding of disease trends, and disease management. Larger population studies of Ph-MPNs from developing countries such as India are required in order to enhance knowledge regarding the clinical and molecular profile of MPN. This is essential in an era of emerging targeted therapies and will help in tailoring patient-centric therapies.

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