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Pocythemia - clinico-laboratory profile and management in a resource limiting setting

KEYWORDS

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ABSTRACT *Background: Janus kinase 2 (JAK 2) mutation is a significant factor in the pathogenesis of Polycythemia Rubra Vera. It is also known to occur in other chronic myeloproliferative disorders like Essential Thrombocythemia. We studied the frequency of JAK 2 mutation in patients with Polycythemia Rubra Vera, compared the clinical and laboratory parameters of patients who were positive and negative for the mutation and management of these patients in a resource limiting setting.*

Methods: All patients with the diagnosis of Polycythemia Vera (PV) according to the British Committee for Standards in Hematology (BCSH) guidelines were included in the study. Clinical andlaboratory parameters of the patients with PV were evaluated. On arriving at the morphological diagnosis the patients were screened for the presence or absence of JAK 2 mutation and comparison among the two groups were carried out.

Results: We studied about 25 patients with Polycythemia Vera over the last two years. The mean age of the cohort group was 56.5±15.5 years. 7 were female patients. On comparing the clinical and lab parameters of the patients with JAK 2 positive and patients with JAK 2 negative, we noticed that JAK 2 positive patients were older by 13.8 years, had higher incidence of elevated haemoglobin, total counts and splenomegaly. The occurrence of thrombotic events was higher in JAK2 positive group, similarly was the incidences of splenomegaly.

Conclusion: The presence of JAK 2 mutation did increase the incidence of thrombotic events though the presentation was a decade older in these patients. Managing these patients in a resource limiting setting was also highlighted in our study.

Introduction

Polycythemia Rubra Vera is a chronic clonal my eloproliferative disorder which is characterized by cytokine independent my eloid precursor proliferation, progressively increasing the red cell mass. This causes hyper viscosity of blood – a major determinant of the circulatory disturbances in these patients. The resulting thrombotic complications are a major cause of morbidity and mortality (1). Many patients have associated high total counts and platelet counts. The Janus kinase 2 point mutation JAK 2 V617F is associated with PRV. Most patients are diagnosed in their fifth or the sixth decade of life, but can occur in any age group. We notice a rising incidence of PRV and other chronic my eloproli ferative disorders over the last few decades. More asymptomatic patients are being diagnosed incidentally. This could probably be secondary to increased availability of laboratory testing(2). There is a potential risk of progression to secondary acute myeloid leukemia or myelofibrosis (3).

There are no curative therapeutic options for PV hence the main objective of treatment is alleviating the symptoms of the patients, reducing the thrombosis risk and avoiding the transformation to leukemia. The current treatment options are phlebotomy, my elosuppressive drugs and interferon alpha (3,4,5,6,7,8). Patients with adequately controlled erythrocyte counts have low mortality with 80% surviving more than 12 years (1,3). This article provides us an insight into the frequency of JAK 2 mutation in patients with PV, highlight the comparison of clinical and laboratory parameters between patients who are positive against those who are negative for JAK2 mutation and the management of PV in a resource limiting setting.

Materials and methods

All patients with chronic myeloproliferative disorder which satisfied the British committee for standards in hematology (BCSH) guidelines (9) for Polycythemia Vera were included in the study from SRMC, Chennai, during 2013-2014. The diagnosis was confirmed by bone marrow aspiration and biopsy in all the patients.

The values of haemoglobin, total counts, and platelet counts were obtained by automated cell counter. JAK 2 was done by PCR method. Marrow iron stores were assessed by Perl's stain and the marrow fibrosis by hemato xyl in and eosin, reticul in stains. Ultrasound with Doppler and or or MRI scans were done for diagnosis of thrombosis as and when required.

History of cardiovascular complications like the presence of DVT, PTE, Acute MI, coronary insufficiency, stroke, TIA or arterial thrombosis were among the other variables evaluated. The presence of cardiovascular risk factors like high lipid levels, T2DM, SHT, smoking habits were also noted. Patients were stratified into two risk groups – low risk and high risk based on age ≤ or ≥60 years and presence or absence previous thrombosis. Statistical analysis for significance could not be arrived in view of low sample size.

Results

The study included 25 patients of which 18 were males and 7 were females with mean age of 56.5 years at diagnosis. The results are summarized in Table 1.

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Table 1: Study Group Characteristics

	Entire cohort	JAK 2 Positive	Jak 2 negative
number	25	9	16
Age (yrs)	56.5±15.5	59.4±12.6	45.2±16.4
Sex			
males	18	7	11
females	7	2	5
Clinical features			
asymptomatic	5	2	3
spleenomegaly	8	6	2
Thrombosis	12	7	5
Evidence of thrombosis			
arterial	8	5	3
venous	4	2	2
Thrombotic risk factors			
T2DM	11	4	7
SHT	15	6	9
Dyslipidemia	9	3	6
Smoking	6	2	4
Lab Parameters			
Haemoglobin	18.8±2.1	20.5±1.6	17.4±1.5
Total counts	13.1±5.2	15.5±4.8	9.3±4.2
Platelet counts	5.51	6.25	4.34
Serum LDH	456	583	316
S.Erythropoeitin	0.86	0.74	0.91
Risk Stratification			
Low risk	4	1	3
High risk	8	4	4
Response to treatment			
Haemoglobin at 10-12 weeks of therapy	13.5±1.8	13.9±1.6	12.7±1.5

The median age of entire patients cohort at the time of diagnosis was 56.5±15.5 years. 4 Patients (16%) were less than 40 years of age, 13 patients (52%) were between 40 and 60 years of age and 8 patients (32%) were more than 60 years of age. 7 Patients (28%) were female patients. The median haemoglobin value was 18.8 mg/dl (range 15.9-22.1). 9 Patients (36%) had high total counts of more than 12000/ cu mm. 17 patients (68%) had high platelet counts of more than 400000/cu mm.8 patients (32%) had history of arterial thrombosis while 4 patients (16 %) had venous thrombosis. 13 Patients (52%) did not have any thrombotic or systemic adverse effects.4 Patients(16%) were low risk and 8 patients (32%) were high risk in relation to thrombosis.

JAk 2 mutation positivity was found in 9 patients (36%). A slight male preponderance was seen in patients with JAK 2positivity. 8 Patients (32%) presented with splenomegaly, while 5 patients (20%) were asymptomatic. Increased cellularity of bone marrow was noted in all the patients. The total counts and platelet counts were higher in the JAK 2 positive group.

After the initial diagnosis, all the patients were managed with phlebotomy to achieve a target haemotocrit of 45%in males and 43% in female patients. The patients were also started on low dose aspirin and Hydroxyurea – to lower or do away with the need for phlebotomies. This therapeutic method was practiced in order to be feasible to the lower socio economic patients who came to the medical college hospital.

Discussion

The identification of JAK 2 mutation – describes its effect on normal hematopoietic stem cells making them more sensitive to erythropoeit in, thrombopoeit in and myeloid progenitor cells. This hypersensitivity further leads to a varied clinical consequences during the course of the disease (10). These are :

(i) Growth of matured megakaryocytes in ET/PV with overproduction of hypersensitive platelets resulting in platelet mediated micro vascular circulatory disturbances. These circulatory disturbances are very sensitive to low dose aspirin, which forms a major therapeutic option.
(ii) Increased erythropoiesis with erythrocytes over production leads to classic PRV. This is characterized by elevated haemoglobin, hematocr it and red cell mass, which is associated with increased arterial and venous thrombotic complications in addition to platelet mediated micro vascular circulatory disturbances of thrombocythemia.
(iii) Slowly progressive myeloid metaplasia in bone marrow and spleen leading to secondary myelofibrosis (10).

In our study male to female ratio was 2.5:1 which was in contrarary to the observations in other studies. The median age at diagnosis in our study group (56.5±15.5 years) was similar to previous European studies (11).

We highlight these issues in our study:

(i) JAK 2 positive group were about a decade older than the negative group.
(ii) Lab profile was characterized by higher values of haemoglobin, total counts and platelet counts in the JAK 2 positive group.
(iii) Incidences of splenomegaly was higher in JAK 2 positive group than JAK 2 negative group
(iv) The incidence of thrombotic events in the JAK 2 positive was higher than the negative groups.
(v) Phlebotomy along with low dose aspirin and hydroxyurea serve as a good therapeutic option for these patients especially in a resource limiting setting, as shown in our study group.

Arterial thrombosis was observed in 32% of patients and 16% patients had venous thrombosis which were similar to the study done by Marchioli et al (12). All our patients were managed with phleboto my together with low dose aspirin and hydroxyurea. This gave a good hematological control. The haemoglobin was brought under control within 10-12 weeks of therapy with haemoglobinmaintained at 13 to 15.5 mg/dl. Arterial thrombotic events were the main complications followed by DVT.

Even with such a small sample size, we observed that the characteristics and outcome were similar to those of patients treated in US and Europe (3,12,13).

Conclusion

Identification of JAK 2mutation on exon 14 identifies most of the patients with PV but JAK 2 negativity doesnot negate a diagnosis of PV. There could still be a mutation in JAK 2 but in exon 12. Widespread availability of cytogenetics at an affordable price would make diagnosis of these uncommon MPN disorders easy. Treatment of PV by means of phlebotomy, low dose aspirin and hydroxyurea made it possible to bring the abnormal erythroid proliferation under control with low risk of disease transformation into secondary leukaemia even in a resource limiting setting. We are continuing the study to analyse more patients and focus on their outcomes.

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