Descriptive Study in Polycythemia Rubra Vera and Evaluation of Management Outcome

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ABSTRACT

Background: Polycythemia Vera (PV) is a myeloproliferative neoplastic disorder involving uncontrolled red blood cell production resulting in elevated red blood cell (RBC) mass. There is a signaling defect leading to an abnormal response to growth factors, and the abnormal clonal line interferes with normal lineage proliferation. The Janus kinase-2 (JAK2) gene involved with intracellular signaling is mutated in 90% of cases of PV. It can occur in all age groups, but the median age of diagnosis is 60 years. Thrombosis considered as the most common cause for morbidity and mortality.

Aim of study: To review the clinical characteristics of a sample of PV patients and their current treatment in addition to assessment of frequency of development of thrombotic events while on treatment.

Patients and method: A hospital based retrospective study was conducted in the hematology outpatient's clinic from different centers in Iraq over a period of 11months (from January 2020 till November 2020). Patient's age more than 18 years old with duration of the disease more than 6 months and all of them were positive for JAKII V617F mutations were included in this study while excluding those who were negative for this mutation. The patients were divided in to low and high risk based on age and leukocyte counts and history of previous thrombosis and presence of cardiovascular risk factors. The response and resistance to treatment with hydroxyurea were evaluated according to ELN definition.

Result: Thirty patients were enrolled in this study. The median age was 60.6±11 years, ranging between 35-78 years. The mean duration of disease was 54± 5.5 months. Headache was the predominant symptom observed in 96.7%, pruritus was experienced in 63.3%.Splenomegaly was seen in 46.7% .Thrombosis at time of diagnosis happened in 13.4%of cases. The most common complication that occurred in this study group was thrombosis in 20% of patients ,16.6% progressed to myelofibrosis and 63.3% of patients were controlled by treatment.

Conclusion: The demographic and some of characteristic of Iraqi PV patients are similar to those from other countries. A good number of patients were controlled with hydroxyurea. Thrombosis is still the commonest complication in patients with PV and occurred mainly in the first 4 years since diagnosis of polycythemia Vera. Median time for development of myelofibrosis was more than 10 year.

Keywords: Polycythemia vera , Thrombosis, JAK 2.

دراسة وصفية لكثره الحمر الحقيقه وتقييم نتائج العلاج

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الخلاصة

الخلفية : كثرة الحمر الحمراء (Polycythemia Vera) هو اضطراب ورمى تكاثرى نقوى يتضمن إنتاج خلايا الدم الحمراء غير المنضبط مما يؤدى إلى ارتفاع كتلة خلايا الدم الحمراء.(RBC) يبدو أن مسببات عملية المرض هى تحفيز و تكاثر الخلايا السرطانية حيث ان هناك عيب فى الإشارارات مما يؤدى إلى استجابة غير طبيعية لعوامل النمو ، ويتداخل الخط النسيلى غير الطبيعى مع تكاثر النسب الطبيعى. تم تحور جين Janus kinase-2 (JAK2) المتورط فى الإشارات داخل الخلايا فى ٩٠٪ من حالات كثرة الحمر الحقيقية. يمكن أن يحدث فى جميع الفئات العمرية ، ولكن متوسط عمر التشخيص هو ٦٠ ، ويعتبر التخثر هو السبب الأكثر شيوعًا للمراضة والوفيات.

هدف الدراسة: دراسة الخصائص السريرية لمرضى PV ومراجعة العلاج الحالى ، وتكرار تطور أحداث الانصمام الخثارى أثناء العلاج ودراسة عدد المرضى الذين يعانون من كثرة الخلايا الحمراء الذين تحت السيطرة؟
المرضى والطريقة: أجريت دراسة بأثر رجعى فى العيادة الخارجية لأمراض الدم من مختلف المراكز فى العراق على مدى ١١ شهرًا (من يناير ٢٠٢٠ حتى نوفمبر ٢٠٢٠). تم تضمين عمر المريض الذى يزيد عمره عن ١٨ عامًا ومدة المرض أكثر من ٦ أشهر وكانت جميعها إيجابية لطفرات JAKIIV617F فى هذه الدراسة مع استبعاد أولئك الذين كانوا سلبيين لهذه الطفرة والمرضى الذين يعانون من كثرة الحمر الثانوية. تمت مناقشة تقييم عامل الخطر لتطور تجلط الدم عن طريق تقسيم المرضى إلى مخاطر منخفضة وعالية بناءً على العمر وعدد الكريات البيض وأيضًا تقييم الاستجابة والمقاومة للعلاج بهيدروكسى يوريا وفقًا لتعريف الجمعية الاوربية (ELN) للاستجابة ومعايير المقاومة للعلاج تمت مناقشته فى هذه الدراسة.
النتيجة : تم تسجيل ثلاثين مريضا فى هذه الدراسة. كان متوسط العمر ٦٠.٦ ± ١١ سنة ، ويتراوح بين ٣٥-٧٨ سنة. كان متوسط مدة المرض ٥٤ ± ٥.٥ شهرًا. كان الصداع هو الأعراض الأكثر انتشارًا التى لوحظت فى ٩٦.٧٪ من المرضى ، تضخم الطحال ٤٦.٧٪ وحدثت الحكة فى ٦٣.٣٪ التخثرعند التشخيص فى ١٣.٤٪.
كانت المضاعفات الأكثر شيوعًا التى حدثت فى مجموعة الدراسة هذه هى تجلط الدم بنسبة ٢٠ ٪ تحدث فى فترات زمنية مختلفة بعد التشخيص ، وثلاثة مرضى (١٦.٦ ٪) يتقدمون إلى التليف النقوى (تليف نخاع العظم) و٦٣.٣ ٪ من المرضى يخضعون للسيطرة والاستجابة للعلاج .فقط٧٠% من المرضى استعملوا مضادات التخثر.
الاستنتاج : الخصائص الديمغرافية وبعض خصائص مرضى PV العراقيين مماثلة لتلك الموجودة فى البلدان الأخرى. تم السيطرة على عدد كبير من المرضى باستخدام علاج هيدروكسى يوريا. لا يزال التخثر من أكثر المضاعفات شيوعا فى المرضى الذين يعانون من كثرة الخلايا الحمراء الحقيقية PV ويحدث بشكل رئيسى فى السنوات الأربع الأولى منذ تشخيص كثرة الحمر الحقيقية. و متوسط الوقت اللازم لتطور التليف النقوى (تليف نخاع العظم) هو أكثر من ١٠ سنوات.

الكلمات المفتاحية : كثره الحمر الحقيقية ، التخثر ، جين جاك ٢ .

INTRODUCTION

Polycythemia Vera (PV) is myeloproliferative neoplasm (MPN) characterized by clonal proliferation of the erythroid, myeloid and megakaryocyte lineages. Mutations of the Janus kinase 2 (JAK2) genes are responsible in a high proportion of cases of PV; JAK2 is a member of the tyrosine kinase family of enzymes[1].The incidence of PV is reported to be 2-3 per 100,000 of the population, with male-female ratio 1.2:1.The median age at onset 55-60 years and although incidence increases with age, PV can occur at any age even, rarely, in childhood [2]. The biology of PV is characterized by clonality and EPO independence. Genome-wide scanning, which compared clonal PV and nonclonal cells from the same individuals, revealed a loss of heterozygosity in chromosome 9p, in approximately 30% of patients. The natural course of PV usually includes three phases: the prepolycythemic phase, polycythemic phase (PP), and post-polycythemic myelofibrosis (post-PVMF)[3].Presenting signs and symptoms may include headache, plethora, pruritus, thrombosis and gastro-intestinal bleeding. Thrombotic episodes are the most common and most important complication in PV, occurring in approximately one-third of PV patients[4]. From one-half to three-quarters of these events are arterial; ischemic strokes and transient ischemic attacks account for the majority of arterial complications.

Most patients can now be diagnosed on the basis of a raised hematocrit (>0.48 for men and>0.46 for women) together with the presence of the JAK2 V617F mutation. According to WHO 2016 criteria the diagnosis requires the presence of all three major criteria or two major and the minor criteria[5].

The macrovascular events are the primary cause of mortality in patients with PV, accounting for 45% of all deaths [6]. Post PV myelofibrosis (MF) occurs in around 10-20% of PV cases at 15 years after diagnosis. The patient may be asymptomatic but often complains of fatigue, dizziness, weight loss and anorexia. In treating PV, the aim is to reduce complications and thus improve survival and ameliorate the symptoms burden. Thromboembolic events are the major cause of morbidity and mortality; consequently, the prevention is the main aim of any treatment strategy[7]. Target level of hematocrit of<45% is widely used, higher level is associated with increased risk of thrombosis [2].Treatment options include phlebotomy, cytoreductive therapy with Hydroxyurea, Anagralide, Interferon alpha and JAK inhibitor.

PATIENTS AND METHODS

A hospital based retrospective study was conducted in the hematology outpatient's clinic from different centers in Iraq over a period of 11months (from January 2020 till November 2020).Verbal consent was obtained from all

patients took part in this study. Thirty patients who were diagnosed to have polycythemia Vera according to the 2016 WHO criteria were included.Sociodemographic data including age, gender, disease duration and medical history of each patient were recorded. Clinical symptoms, signs and laboratory data of all patients at time of presentation and during follow up were noted, abdominal ultrasound was done for all patients. JAK 2 mutation analysis was done by PCR, bone marrow aspirate and biopsy was done for most of the patients.

Controlled and response criteria were assessed according to 2013 International Working Group – Myeloproliferative Neoplasm Research and Treatment (IWG-MRT) and European Leukemia Net (ELN) [8] that included four criteria complete and partial remission (which incorporate clinical, hematological, and histological response assessments that include a standardized symptom assessment form and consider absence of disease progression and vascular events) ,no response which is any response that does not satisfy partial remission and progressive disease define as transformation into postpolycythemic myelofibrosis and acute myeloid leukemia.

Statistical Analyses

Data were analyzed using statistical package for the social sciences (SPSS version 23) computer software program.

Descriptive statistics presented as frequency tables, Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. Analytic statistics as fisher exact test to find association between two categorical variables because chi-square was inapplicable due to small sample size. Statistical survival analysis was done by Kaplan-Meier test. The P value below or equal to 0.05 was considered to indicate statistically significant difference.

RESULTS

A total of 30 patients were enrolled in this study, male to female ratio was 1.5:1, and the mean ±SD age at diagnosis was 60.6±11 years, ranging between 35-78 years. The mean duration of disease was 54± 5.5 months, ranging between 12 months to 216 months and median 24 months, (table 1). The mean duration of treatment in current study was 50 ±56.1 months (median duration was 24 months). The clinical features of , the hematological picture and the treatment lines of the studied group of patients is given in (tables 2,3,4)The adverse effects of hydroxyurea were shown in (table 5) . Disease control status shown in figure 1and time from diagnosis until development of first thrombotic events is shown using Kaplan meier plot, figure 2,type of thrombotic events observed in this study shown in table 6.

Table 1 Age and gender distribution among studied patients.

Variables		Number	Percentage
Gender	Male	18	60%
	Female	12	40%
Age	<40 years	2	6.7%
	40-59 years	10	33.3%
	≥60 years	18	60%
Duration of disease	12 months	7	23.3%
	>12 months - ≤24 months	8	26.7%
	>24 months	15	50%

Table 2 Clinical evaluation of studied group at diagnosis.

Clinical features		Number	Percentage
Headache	Positive	29	96.7%
	Negative	1	3.3%
Pruritus	Positive	19	63.3%
	Negative	11	36.7%
Paresthesia	Positive	14	46.7%
	Negative	16	53.3%
Abdominal pain	Positive	9	30%
	Negative	21	70%
Blurred vision	Positive	9	30%
	Negative	21	70%
Plethora	Positive	11	36.7%
	Negative	19	63.3%
Epistaxis	Positive	2	6.7%
	Negative	28	93.3%
Hypertension	Positive	10	33.3%
	Negative	20	66.7%
Splenomegaly By ultrasound	Absent (<10cm)	16	53.3%
	Moderate (11-20 cm)	14	46.7%
	Sever (>20cm)	0	0
History of Thrombosis	Negative	26	86.6%
	Venous	2	6.7%
	Arterial	2	6.7%
Risk group on diagnosis	Low risk	11	36.7%
	High risk	19	63.3%

Table 3 Baseline hematological investigation for the patients.

Hematological markers	Mean ±SD	Minimum	Maximum
WBC	12.3± 4.2	6.1	21
Hematocrit	52.1 ±5.6	48	75
Platelet	442.5 ±108	300	865
Hb	18.5 ±1.3	17	24

SD, standard deviation,WBC, white blood cell, HB ,hemoglobin

Table 4 Treatment lines for studied patients.

Treatment line	Number	Percentage
Hydroxyurea	30	100%
Aspirin	15	50%
Ruxolitinib	2	6.6%
Warfarin	5	16.6%
Interferon	1	3.3%
Apixaban	1	3.3%
Phlebotomy	11	36.7%

Table 5 Adverse effects of hydroxyurea.

Adverse effect		Number	Percentage
Non-Hematological	Aphthous stomatitis	2	6.7%
	Diarrhea	2	6.7%
	Nausea	6	20%
	Vomiting	2	6.7%
	Skin pigmentation	5	16.7%
	Leg ulcer	1	3.3%
	Epigastric pain	2	6.7%
	mucositis	1	3.3%
Hematological	Neutropenia (grade1)	3	5%
	Anemia(grade 2)	2	6.7%

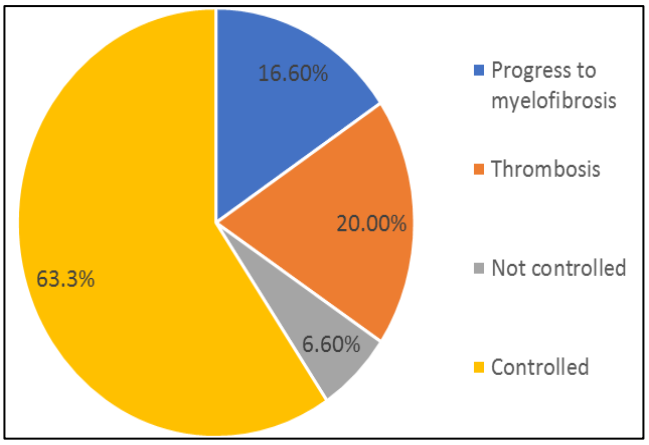

Figure 1 Disease control status.

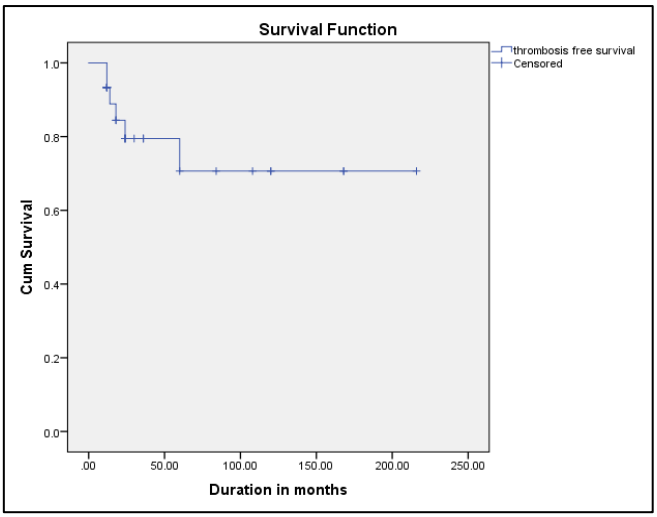

Figure 2 Times to first Thrombotic events

Table 6 Types of thrombotic events observed in this study

Type of thrombosis	At diagnosis	After diagnosis
Arterial		
Myocardial infarction	1 (3.33%)	2 (6.66%)
Cerebrovascular accident	1 (3.33%)	1 (3.33%)
Venous		
Deep vein thrombosis	1 (3.33%)	1 (3.33%)
Portal vein thrombosis	1 (3.33%)	2 (6.66%)
Total	4 (13.4%)	6 (20%)

DISCUSSION

Thirty patients diagnosed with polycythemia Vera have been followed at different Iraqi hematology outpatient's were included

This limited number of patients in this study was due to outbreak of COVID 19 that abstain them from consulting the outpatients hematology clinics, also we excluded 5 patients due to lack of full investigation that needed for diagnosis and 2 patients had duration of disease less than 6 months .

This study showed the mean for age was 60 ranging from 35 – 78 years , there was slight male gender preference with male to female ratio 1.5:1 and the mean duration of the disease was 54±5 months with median duration 24 months which is similar to that of the US study Grunwald et al. 2019 [9].

In this study the most common presentation was headache 96.7% and pruritus in 63% which is concordant with the study from Pakistan, Sultan et al, 2016 [10]; splenomegaly was seen in 46.7% and plethora was observed in 36.7% as compared to study from Egypt in which splenomegaly was observed in 32.2% of cases, Mattar et al ,2013[11].

Thrombotic events at presentation were noted in 13.4% which include both arterial and venous thrombosis (6.7% for each respectively), each patient with thrombotic events has hemoglobin level ≥ 18.5g⁄dL at presentation. In a study from Thailand thrombotic manifestations were prevalent in 29% of cases ,Duangnapasatit et al, 2015[12]. Small sample size in this study may contribute to this result. One patient with thrombotic event at diagnosis was of young age with no previous cardiovascular risk factor.

The mean hemoglobin level in this study was 18.5 ±1.3 g⁄dl in similar to a large study in Europe, Palandri et al; 2019 [13].

Around one third of patient enrolled in this study were treated with phlebotomy while hydroxyurea was used for all patients and one patient was treated with interferon alpha and two of them were treated with ruxolitinib.

Treatment with hydroxyurea showed significant reduction in hematological parameter during first year from diagnosis which was concordant with study from Brazil Linardi et al. 2008[14]. nineteen patients (63.3%) Nineteen patients were at high risk for development of thrombotic events. Nine patients (30%) were not using anticoagulant or antiplatelet therapy, non-compliance was the main reason; however none of them developed thrombotic events during the follow up period.

During follow up we observed that thrombotic events after starting treatment developed in six patients (20%) at different time points even after achievement of hematological control (hematocrit ≤ 45 %) and most of these events developed during first four year of diagnosis ,in addition to PV most of these patients have cardiovascular risk factors . In a large study from Europe, 36 patients developed thrombosis , Palandri et al; 2019 [13] .Three patients (16.6%) in this study progressed to myelofibrosis all of them had a duration of PV of more than ten years. In similar studies, 5.56% of patients developed myelofibrosis in a study from Egypt , Mattar et al ,2013 [11] and 29 cases (12.6%) developed myelofibrosis in a study from Europe, Palandri et al;2019 [13].

According to response criteria (2013 IWG-MRT and ELN response criteria); 63.3% of patients in this study achieved control in which hematocrit was below 45%, while non-control was seen in 6.6%. Most of the patients who were using hydroxyurea tolerated it although some of them suffered from gastrointestinal side effects ,resistance to hydroxyurea developed in two patients (failure to control hematocrit and leukocytosis , failure to reduce splenomegaly and ⁄or symptoms)in comparison to the study from Europe, Palandri et al; 2019 [13],which showed good control in 28.6%, no response in 19% of patients.

CONCLUSION

The demographic and characteristics of Iraqi PV patients are rather similar to those from other countries. A good number of patients were controlled with hydroxyurea. Thrombosis occurred mainly in the first 4 years since diagnosis of polycythemia Vera .Median time for development of myelofibrosis was more than 10 year.

Limitation

Small sample size, and short period of study.

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