

Treatment outcome of Philadelphia chromosome negative myeloproliferative neoplasms: experience of a single developing country's hematology-oncology centre

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Abstract

Background: Myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are characterized by excessive production of blood cells. Treatment of MPNs patients has an important effect thereby reducing morbidity and mortality.

Objective: To evaluate the effect of cytoreductive treatment on some hematological and biochemical parameters in MPNs patients treated at a hemato-oncology Centre in Erbil, Iraq.

Methods: A total of 185 patients diagnosed with PV, ET, and PMF (111 males and 74 females with a mean age of 50.8 ± 3.2 years, range: 46-73) were assigned to receive MPNs treatment. Laboratory tests were performed before and after a median period from the initiation of MPNs treatment of 9.3 months (range 5-10 months).

Results: Significant differences were noted in Hemoglobin ($P < 0.003$), Hematocrit ($P < 0.004$), Neutrophil ($P < 0.001$) and glutamate pyruvate transferase levels ($P < 0.01$) in PV patients, Platelet count ($P < 0.002$) in ET patients, and both white blood cell count ($P < 0.004$) and Lactate dehydrogenase level ($P < 0.001$) in PMF patients, while no significant differences were found in other parameters at the time of diagnosis and during therapy.

Conclusion: Clinical and laboratory improvements were presented in MPNs patients. Regular follow up of patients are essential to ensure prescribed treatment in addition to the continual and long-lasting response to therapy and to prevent thrombosis.

Keywords: Cytoreductive treatment, MPNs, JAK2 mutation.

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Introduction

The classic myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). They are characterized by excessive terminally differentiated myeloid cells¹, when there is a need for myelosuppression, the antineoplastic activity has been increasingly used, based on inhibition of the ribonucleotide reductase enzyme and hence the DNA synthesis is inhibited². Currently, this is the most frequently prescribed drug for the treatment of MPNs

worldwide and is considered as an essential medicine by the World Health Organization (WHO) with a broad dose response range, little mutagenic risk, and mild side effects³.

Since 2005, the major interest has been generated in the Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) and anti-JAK2-targeted therapy⁴. Mutated Janus Kinase 2 (JAK2) V617F is found in approximately 95% of patients with PV, and about 50% of those with ET or PMF⁵.

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Thus, MPNs are clinically heterogeneous diseases in which drugs are used to lower red blood cell (RBC), white blood cell (WBC), and Platelet (Plt) counts or to inhibit Plt function is often problematic⁶. Hydroxyurea (HU) reduces the Plt count, thereby decreasing thrombotic episodes in patients with ET. Because of the proven efficacy

of HU in MPNs treatment, HU has been used in clinical trials on a wide range of advanced MPNs⁷. These diseases are often accompanied by a profound clinical and laboratory profile that significantly reduces survival and quality of life of patients. In general, HU has been shown to reduce MPN-related symptoms including fatigue, night sweats, pruritus, concentration problems and splenomegaly. Additionally, it also reduces morbidity and mortality risk factors such as thrombotic events and fibrotic and/or leukemic transformation^{8,9}.

It has been noticed that therapeutic interventions focusing on hematological and biochemical levels are beneficial in the prevention of MPNs risk factors and symptoms. The correlation between JAK2 V617F mutation with laboratory and clinical features of the disease through MPNs treatments is interesting¹⁰.

Nowadays, after molecular identification of JAK2 V617F mutation in patients diagnosed for MPNs particularly PV, ET, and PMF are currently drawing scientific attention for JAK2 V617F mutation study and its potential influence on disease phenotype¹¹.

Currently, the most important objectives are in slowing or delaying progression of disease and prevention of vascular/thrombotic events. Myelosuppressive drugs induce hematological responses in MPNs and can reduce splenomegaly, as well as relieve constitutional symptoms¹².

A subset of patients in this study reported symptom relief as their most important treatment goal. The therapies that patients most often reported receiving at any time were phlebotomy 34 (18.3%), aspirin 41 (22.1%), and HU 32 (17.3%) in the PV patients; ASA 25 (13.5%), and pegasys 24 (12.9%) in ET patients; and aspirin 14 (7.5%), ruxolitinib 5 (2.7%) and HU 10 (5.4%) in the PMF patients.

There is a lack of outcome data about MPNs patients who have been treated at our Centre. Consequently, the aim of the present study was to evaluate the effect of cytoreductive treatment on some hematological and biochemical parameters in MPNs patients treated at one Hemato-Oncology Centre in Erbil, Iraq.

Methods

Blood patients

This retrospective study had 185 consecutive patients with MPNs, (111 males and 74 females with a mean age

of 50.8 ± 3.2 years, range: 46-73), Patients were diagnosed and categorized into PV, ET, and PMF using revised WHO 2016 criteria¹³, there were 107 patients with PV, 49 patients with ET, and 29 patients with PMF. These included both newly diagnosed cases (n=41) and previously diagnosed cases on follow-up (n=144). They were enrolled in the trial and treated for myelosuppression. Patients were excluded if they did not fulfill WHO criteria and if they did not attend follow-ups regularly. The study was conducted between October 2016 and July 2017.

From each individual, 5 ml the blood samples were obtained. Patients were selected among those followed up in the hematology clinic at Nanakali Hospital for blood diseases and cancer in Erbil, Iraq and who were referred to the laboratory undergo hematological and biochemical tests. Blood samples were subjected to analysis for JAK2 V617F mutation using Amplification Refractory Mutation Screening Polymerase Chain Reaction ARMS-PCR technique¹⁴.

For data collection a case report form was prepared which is consisted of demographic features, patient characteristics, and laboratory data at the time of diagnosis and during therapy [after a mean duration of response was 9.3 months (range 5-10 months)]. The study was approved by the scientific advisory committee of the College of Medicine at Hawler Medical University and written informed consent was obtained from all patients before their inclusion in this study (Ethical no: 17 in 23/4/2016).

All patients recruited into the study were fully anonymized, and received the MPNs treatment. PV and ET patients were on ASA (aspirin: acetyl salicylic acid), Venesection (Phlebotomy), Pegasys (pegylated interferon-alfa-2a), HU (hydroxyurea), and Plavix, PMF patients were on Jakafi (ruxolitinib), Danazol (reduce pain), and Exjade (deferasirox; reduce iron) depending on the type and severity of the diseases. The starting dose of myelosuppressive drugs was subsequently modified according to the efficacy and tolerability in each patient. Therefore, a maintenance dose of the drugs was administered to maintain the laboratory results within normal ranges.

Haematological parameters

Blood counts were measured using autoanalyser. The PE-600, fully auto Hematology Analyzer (China) was used, while Excite-40 ESR analyser was used to analyse ESR (Vital Diagnostics, USA).

Biochemical parameters

Blood sodium, potassium, chloride and ionized calcium were measured simultaneously by OPTI LION Electrolyte auto analyzer in the same single-use cartridge. Moreover, other biochemical tests were estimated with fully automated chemical analyzer by using Cobas diagnostic kits (Roche/COBAS 311 INTEGRA, biochemical analyzer).

Statistical analysis

Data were expressed as the mean $\pm$ the standard deviation

SD, or as percentage frequencies. All calculations were made using (SPSS for windows version 19.0). Within patient comparisons were made using the student t-test for paired data, at a significance levels of $P < 0.0515$.

Results

The age range of the 185 evaluated patients was 46-73 years with a mean of 50.8 ± 3.2 years. Male patients were 60% (n=111) and female patients were 40% (n=74). The sample included 57.8% (n=107) PV patients, 26.4% (n=49) ET patients, and 15.6% (n=29) PMF patients, as shown in Table 1.

Table 1: Different variables of the studied groups.

Variables	PV	ET	PMF	Total
Number of patients	107 (57.8%)	49 (26.4%)	29 (15.6%)	185
Age (year, mean $\pm$ SD)	49.7 $\pm$ 2.3	51.2 $\pm$ 2.8	54.3 $\pm$ 4.3	50.8 $\pm$ 3.2
Gender (%)				
Male	75 (70.7%)	19 (38.3%)	17 (58.8%)	111 (60%)
Female	32 (29.3%)	30 (61.7%)	12 (41.2%)	74 (40%)
Number of patients with splenomegaly	22	19	11	52

A total of 52 patients had splenomegaly at the start of therapy, and three patients underwent splenectomy for symptomatic splenomegaly.

At the end of the study period, the majority of the mean

values of hematological and biochemical parameters were within normal limits. The presence of normal hematological and biochemical values indicated the efficacy of the treatment.

Table (2): Hematological parameters at time of incidence and during MPNs therapy.

Variables	PV		P value	ET		P value	PMF		P value
	At time of diagnosis	During therapy		At time of diagnosis	During therapy		At time of diagnosis	During therapy	
WBC (X10 ⁹ /L, mean $\pm$ SD)	18.8 $\pm$ 0.8	10.1 $\pm$ 0.59	0.06	8.9 $\pm$ 0.89	10.1 $\pm$ 0.99	0.07	9.7 $\pm$ 0.12	8.3 $\pm$ 0.26	0.004
Hgb (X10 ⁹ /L, mean $\pm$ SD)	18.6 $\pm$ 0.57	14.4 $\pm$ 0.03	0.003	13.8 $\pm$ 0.62	13.2 $\pm$ 0.72	0.42	11.8 $\pm$ 0.91	12.7 $\pm$ 0.06	0.44
HCT (% , mean $\pm$ SD)	59.3 $\pm$ 2.53	46.4 $\pm$ 1.23	0.004	46.3 $\pm$ 2.63	43.5 $\pm$ 2.7	0.46	35.1 $\pm$ 2.0	36.3 $\pm$ 1.09	0.43
Plt (X10 ⁹ /L, mean $\pm$ SD)	348.2 $\pm$ 20.8	394.1 $\pm$ 15.8	0.8	687.7 $\pm$ 21.5	400.4 $\pm$ 24.0	0.002	291 $\pm$ 12.3	251.2 $\pm$ 8.9	0.09
Neutrophil (% , mean $\pm$ SD)	79.7 $\pm$ 3.39	73.8 $\pm$ 3.28	0.001	82.0 $\pm$ 2.24	78.1 $\pm$ 3.23	0.72	76.3 $\pm$ 3.49	73.9 $\pm$ 3.73	0.41
Lymphocyte (% , mean $\pm$ SD)	14.7 $\pm$ 1.41	20.4 $\pm$ 1.13	0.11	12.4 $\pm$ 1.51	15.3 $\pm$ 1.7	0.81	21.5 $\pm$ 1.45	22.9 $\pm$ 1.9	0.23
Monocyte (% , mean $\pm$ SD)	4.2 $\pm$ 0.17	4.1 $\pm$ 0.9	0.17	4.1 $\pm$ 0.1	4.2 $\pm$ 0.66	0.71	3.7 $\pm$ 0.1	3.8 $\pm$ 0.28	0.73
Eosinophile (% , mean $\pm$ SD)	2.4 $\pm$ 0.87	2.2 $\pm$ 0.74	0.83	2.4 $\pm$ 0.7	3.6 $\pm$ 0.09	0.81	4.1 $\pm$ 0.2	1.4 $\pm$ 0.7	0.11
ESR (%)	30.5 $\pm$ 1.3	21.9 $\pm$ 1.65	0.61	10.2 $\pm$ 0.02	6.5 $\pm$ 0.1	0.08	62 $\pm$ 2.4	45.9 $\pm$ 2.9	0.34

Table 3: Biochemical parameters at time of incidence and during MPNs therapy.

Variables	PV		P value	ET		P value	PMF		P value
	At time of diagnosis	During therapy		At time of diagnosis	During therapy		At time of diagnosis	During therapy	
SerumGlucose (mg/d,mean±SD)	145±5.4	110±5.2	0.6	130±4.7	105±4.5	0.06	119±4.4	112±3.1	0.17
Urea (mg/dl,mean±SD)	52.1±3.5	45.8±2.7	0.26	40.3±2.2	41.2±2.6	0.44	35.4±1.8	36.2±1.1	0.44
Creatinine (mg/dl,mean±SD)	1.3±0.07	1.12±0.05	0.44	0.99±0.03	0.9±0.02	0.45	1.0±0.02	1.1±0.03	0.54
Uric acid (mg/dl,mean±SD)	6.1±0.07	5.3±0.05	0.36	4.7±0.1	4.3±0.11	0.63	5.1±0.2	4.8±0.3	0.41
GOT (IU/L,mean±SD)	30.4±1.0	26.2±1.1	0.91	30.1±1.3	26.1±1.2	0.78	20.8±1.01	22.1±0.9	0.18
GPT (IU/L,mean±SD)	25.9±1.2	21.3±1.1	0.01	22.1±1.9	19.4±1.9	0.83	19.8±1.73	19.5±1.0	0.32
Total Bilirubin (mg/dl,mean±SD)	0.2±0.03	0.9±0.04	0.15	0.83±0.04	0.80±0.05	0.99	0.99±0.04	1.23±0.06	0.28
Direct Bilirubin (mg/dl,mean±SD)	0.48±0.06	0.32±0.04	0.15	0.23±0.07	0.21±0.07	0.8	0.47±0.03	0.38±0.03	0.73
ALP (IU/L,mean±SD)	220.9±6.9	220.6±8.2	0.72	179.3±6.4	215±5.5	0.76	149.6±4.6	151.9±4.0	0.18
LDH (IU/L,mean±SD)	551±17.2	458±15.2	0.39	567±20.3	452±20.4	0.12	498±18.62	371±15.0	0.001
Na ⁺ (mmol/L,mean±SD)	139±4.6	139.6±5.3	0.56	142±4.19	140.2±3.2	0.29	141.3±4.25	138.1±3.17	0.28
K ⁺ (mmol/L,mean±SD)	4.44±0.04	4.6±0.04	0.88	4.83±0.044	4.73±0.06	0.63	4.6±0.07	4.53±0.06	0.51
Cl ⁻ (mmol/L,mean±SD)	109±3.9	108±3.1	0.68	118±2.1	110±1.4	0.26	114±2.7	108±3.7	0.07
Ca ⁺² (mg/dl,mean±SD)	9.09±0.09	7.93±0.3	0.61	8.4±0.09	6.86±0.01	0.54	8.8±0.01	9.2±0.08	0.68
TC (mg/dl,mean±SD)	154±4.4	136.7±2.3	0.23	156±3.5	167±3.2	0.4	119±3.73	101.8±3.9	0.71
TG (mg/dl,mean±SD)	143.2±2.0	126±33.7	0.19	172±4.1	134±3.0	0.78	122±3.1	75.3±2.1	0.65
HDL-C (mg/dl,mean±SD)	47.3±1.5	41±1.4	0.18	43.7±1.9	45.4±1.3	0.74	33.9±1.34	34.6±1.6	0.89
LDL-C (mg/dl,mean±SD)	69.4±1.8	56.3±1.3	0.21	71.9±1.9	78.3±1.9	0.22	90.8±1.1	52.1±1.2	0.1

The mean values of hematological and biochemical parameters were shown in Tables 2 and 3. Values at the time of diagnosis were compared with those during therapy; the PV patients showed significantly higher levels of hemoglobin ($P<0.003$), hematocrit ($P<0.004$), Neutrophil ($P<0.001$), and glutamate pyruvate transferase (GPT) ($P<0.01$), in ET patients had significantly ($P<0.002$) higher platelet counts, and PMF patients had significantly higher Lactate dehydrogenase level ($P<0.001$) and white blood cell count ($P<0.004$). These findings were out of the 27 parameters evaluated.

Finally, no significant differences in some hematological and biochemical parameters were observed at the time of diagnosis and during therapy.

Discussion

The biggest challenge to-date is to find a way for MPNs complete cure but, the goal of therapy is preventing and/or treating thrombotic events, hemorrhages, and maintaining hematological and biochemical test levels within normal ranges¹⁶.

When clinicohematological data were compared in different subtype MPNs at time of diagnosis and during therapy,

our study results has shown that treatment of MPNs has variable effects on some hematological and biochemical parameters. Therapy is effective in the prevention of risk factors including thrombotic events. Hemoglobin, Hematocrit, Neutrophil and Glutamate pyruvate transferase levels in PV patients lowered significantly; in ET patients there was a significant reduction in Platelet count, and in PMF patients both Lactate dehydrogenase and White blood cell levels were lowered significantly. These findings in our study are similar to those conducted by Zalcberg et al¹⁷ and Soyer N et al¹⁸, who reported that treatment of MPNs was associated with lower blood counts.

Abdullah et al¹⁹ conducted a study in Iraq, observed significant differences in WBC, and Plt counts, whereas in RBC, PCV, and Hb counts, revealed highly significant differences in MPNs patients. Moreover, our results are in accordance with the previously published study showing in MPN subjects positive for JAK2 V617F mutation an increased chemosensitivity to therapy²⁰.

Furthermore, a study conducted by Silva-Pinto et al²¹, on sickle cell patients revealed that patients presented clinical and hematological improvements after cytoreductive therapy.

The study results of Ha JS et al²², disagree with our findings, who reported that treated and untreated ET patients with the JAK2V617F mutation had higher hemoglobin and leukocyte concentrations.

No significant differences in the remaining hematological and biochemical parameters were observed in our study.

The exact mechanism of the therapy remains unknown, but various authors speculate that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein. Beneficial effects of HU include decreasing neutrophils and increasing the water content of erythrocytes. Alternatively, treatment of MPNs including hydroxyurea has been found to have many various side effects such as granulocytopenia and anemia, especially after long-term therapy²³. However, inhibitors of the JAK2/STAT pathways cannot be expected to block cytokine production completely and signaling in MPNs²⁴.

Moreover, no significant differences were found in plasma lipid profile, renal function, liver function, and electrolyte tests. These results were similar to results of previous studies²⁵. Furthermore, a study by Ginsberg et al²⁶, indicated increased lipid profile levels in MPNs patients after therapy.

Conclusion

Finally, current therapies for MPNs still need improvement in the area of patient's quality of life, reduction of cardiovascular complications, and prevention of hematological progression. Further studies are required to evaluate the potential for quality of life effects from MPN treatments. A better understanding through clinical and experimental studies of the alterations in the hematological and biochemical values of patients with MPNs is important from a practical point of view and may enable in the planning of more precise treatment.

Conflict of interest

All authors have no conflict of interest.

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