Original Article

The Jak2 V617 Mutation Triggers Erythropoiesis And Patients Presented With Good Hemoglobin Level In Idiopathic Myelofibrosis (IMF)

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Objective: To document the impact of JAK2 mutation on haemoglobin(Hb) level in patients with IMF.

Methods: Thirty five patients were studied in which 19 patientswere JAK2 positive and 16 patients were JAK2 negative. Sample collection technique was purposive non-probability sampling. Variations were observed among the studied JAK2 positive and JAK2 negative patients regarding haemoglobin level.

Results: The total haemoglobin level was compared in between JAK2 positive and negative patients. In JAK2 positive and negative patients mean haemoglobinlevel was 10.6g/dl and 8.6g/dl respectively.

Conclusion: Due to the better haemoglobin level, patients with JAK2 mutation have less transfusion requirements and partially protect against severe anemiaas compared to patients with no mutation.

Key Words: Myeloproliferative disorder,Idiopathic myelofibrosis, Haemoglobin.

Introduction

Myeloproliferative disorders (MPD) are clonal disorders of haemopoiesis that lead to an increase in numbers of one or more mature blood cell progeny. All MPDs arise as a somatic mutation of pluripotent haemopoietic stem cell.[1,2] In MPDs the proliferative capacity of neoplastic stem cell is not properly controlled and excessive haemopoiesis occurs initially.[3] Idiopathic Myelofibrosis (IMF) is a Philadelphia chromosome (Ph) negative clonal MPD of the pluripotent haemopoietic stem cell (HSC), in which a clonal proliferation of multiple cell lineages is accompanied by progressive bone marrow fibrosis.[4] IMF is characterized by anaemia, splenomegaly, immature granulocytes, erythroblast, tear drop red cells in the blood and bone marrow fibrosis. In the year 2005, several researcher groups reported a single, acquired point mutation in the Janus kinase 2 (JAK2) genes in the majority of patientswith Phnegative MPDs. JAK2 mutation plays a vital role in the pathogenesis of Ph negative MPDs. JAK signaling is activated in haematological malignancies by a number of mechanisms including the down regulation of negative regulators of JAK-STAT pathways, amplification of the JAK2 locus, and involvement of JAK2 in chromosomal translocations and by identification of an activating point mutation in JAK2. In the mutation of JAK2 there is a substitute of bulky phenyalanine for a conserved valine at position 617. Mutation in the JAK2 causes activation of stats in the absence or in the presence of only trace quantities of haemopoietic growth factor.[5]

The objective of this study was to observe and compare the haemoglobinconcentration (Hb) in between JAK2 and negative patients.

Patients and Methods

This study was conducted at the Armed Forces Institute of Pathology (AFIP), Rawalpindi. It was a comparative and cross sectional study and sampling was done by purposive non-probability technique. The study was conducted from January 2004 to December 2008. The project was approved by the ethical committee of AFIP, Rawalpindi. An informed consent was taken from the patients who were studied prospectively. In return, the patients received their JAK2 result free of cost. A total of 35 patients diagnosed with IMF at the Department of Hematology, AFIP, Rawalpindi, were studied. The patients were included irrespective of age, sex and socio-economic status. The patients of IMF diagnosed by conventional criteria were included in this study and their blood samples were collected for JAK2 mutation analysis and blood complete picture. Patients with secondary myelofibrosis (hairy cell leukaemia, acute leukaemia, metastatic carcinoma, disseminated tuberculosis and lymphoma etc)and patients on treatment were excluded from the study. Blood sample (3mL) was taken under aseptic condition in CP bottles containing EDTA anticoagulant. The blood count, including the white cell count, Hb, mean cell volume, mean cell haemoglobin and platelets counts were carried out on haematologyanalyser Sysmex KX-21. Gene analysis for JAK2 mutation was carried out by

Newton et al, 1989). The target DNA was amplified using the primer complementary to the JAK2 mutation. A set of three primers was used. JAK2 mutant allele was amplified by a common reverse primer (5'-CTGAATAGT ACAGTGTTTTCAGTTTCA) and a forward specific primer (5'-AGCATTTG GTTTTAAATTATGGAGTATATT) produc ing 203bp amplified product. The common reverse primer and a forward control primer (5'-ATCTATAGTCATGCTGAAA GTAGGA GAAAAG) was used to amplify a 364bp product that served as PCR internal control. Polyacry- lamide gel was used to amplify the products.

Result

The data was entered in statistical package for social sciences SPSS (version 12.0) and the same software was used for statistical analysis. A total of 35 patients with idiopathic myelofibrosis were studied. Out of 35 patients, 19 (54.3%) were JAK2 positive and 16 (45.7%) patients were JAK2 negative. The Hb level was compared in between JAK2 positive and negative patients. In JAK2 positive patient'sHb level was 10.6g/dl. In the JAK-2 negative patients Hb level was 8.6g/dl.

Discussion

MPDs are clonal disorders of haemopoiesis. The MPDs can be either Ph positive or Ph negative. The Ph positive MPD is chronic myeloid leukaemia while the Ph negative MPDs are polycythaemiarubravera, essential thromb ocythaemia and IMF6, 7.IMF has characterized by anaemia, splenomegaly, immature granulocytes, erythroblast, tear drop red cells in the blood and bone marrow fibrosis. The haematological features (Hb level) of idiopathic myelofibrosis have not been studied in Pakistan before. The JAK2 mutation plays a significant and independent influence on the disease phenotype. It is correlated with the expansion of clonal haematopoietic cells. Some previous studies have also focused on the phenotype of JAK2 positive and JAK2 negative patients and have concluded that phenotypically, the JAK2 mutation positive patients are different from the JAK2 negative patients. The patient's positive for JAK2 mutation had higher haemoglobin level (10.6g/dl) as compared to JAK2 negative patients (8.6g/dl). Due to the better haemoglobin level, JAK2 positive patients have less transfusion requirem- ents. Similar findings were also observed in another study that also observed that the haemogl- obin level in JAK2 positive patients is higher than in the JAK2 negative patients. Because of this mutation patients may be able to partially protectagainst severe anemia.

Conclusion

Due to the better haemoglobin level, JAK2 positive patients have less transfusion requirements so partially protect against severe anemia.

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