ORIGINAL ARTICLE

DEMOGRAPHIC FEATURES OF CHRONIC MYELOPROLIFERATIVE NEOPLASMS PRESENTING AT SHAIKH ZAYED MEDICAL COMPLEX, LAHORE

AMMAR T. AND AZIZ M.
Department of Hematology, Shaikh Zayed Hospital, Lahore – Pakistan

ABSTRACT

Background and Objectives: The term myeloproliferative neoplasms (MPN) was first introduced by William Dameshek in 1951 to emphasize the clinicopathological similarities between chronic myeloid leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), and with myeloid metaplasia (MMM) (Also known as, chronic idiopathic myelofibrosis or primary myelofibrosis) Accordingly, these 4 disorders are currently referred to as "classic" MPN. However, several CMPN-like clinicopathological entities have since been described and, at present the World Health Organization (WHO) system for classification of myeloid neoplasms organize classic MPN as a completely separate category. The objective of the study was to evaluate the demographic features of chronic myeloproliferative neoplasms (CMPN).

Methods: Cross-sectional descriptive study was carried out at Haematology Department, Shaikh Zayed Hospital, Lahore from 4th April 2007 to 4th April 2013. This study comprised of two hundred (200) patients. Patients aged 16 years and above, both genders and diagnosed cases of CMPD were included. Standard procedures were followed for all laboratory tests.

Results: In this study 200 patients of CMPN were diagnosed. CML was found to be the commonest and ET was least common. In CML peak incidence was in 4th decade with male preponderance and mean age was 40 years. In IMF mean age was 55 years and peak incidence was in 6th decade while female preponderance was seen. In PRV mean age was 64 years and female preponderance was noted with peak incidence in 7th decade. In cases of ET mean age was 67 yrs, all patients were male and peak incidence was in 7th decade.

Conclusion: In this study among CMPN Chronic Myeloid Leukemia is commonest of all and Essential Thrombocythemia was found to be least common. Their demographic features were found to be close to international studies. The only difference was female preponderance in IMF in our study while other studies have shown male preponderance.

Key words: Demographic features, Myeloproliferative disorders, Thrombocytosis.

INTRODUCTION

Myeloid disorders constitute a subgroup of hematological malignancies that is separate from lymphoid disorders. The World Health Organization system for classification of tumors of the hematopoietic system divides myeloid disorders into acute myeloid leukemia and chronic myeloid disorders which include Myeloproliferative neoplasms as one subtype.[1]

The term myeloproliferative neoplasms (MPN) was first introduced by William Dameshek in 1951 to emphasize the clinicopathological similarities between chronic myeloid leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), and myeloid metaplasia (MMM) (Also known as, chronic idiopathic myelofibrosis or primary myelofibrosis).[2] Accordingly, these 4 disorders are currently referred to as "classic" MPN. However, several CMPN-like clinic-pathological entities have since been described and, at present the World Health Organization (WHO) system for classification of myeloid neoplasms organize classic MPN as a completely separate category.[4] are clonal disorders of haemopoiesis that lead to an increase in the numbers of one or more mature blood cell progeny. In CMPN common disorders include polycythemia vera (PV), essential thrombocythemia (ET), idiopathic myelofibrosis (IMF) and chronic myeloid leukemia (CML). These disorders share clinical, morphological and molecular features and can transform in their course to one another and into acute leukemia. CML results from an acquired genetic defect character-rized by expansion of myeloid cell mass replacing nor-mal haemopoiesis.[5]

Polycythemia vera (PV), idiopathic myelofibrosis (IMF), and essential thrombocytosis (ET) have been traditionally classified under the "the non CML chro-

Corresponding Author: Dr. Tooba Ammar
Department of Hematology, Shaikh Zayed Hospital, Lahore
E-mail: doctooba@gmail.com Cell: 03214011553

nic myeloproliferative neoplasms"[2] because they share the features: involvement of a multipotent hematopoietic progenitor cell.[6] Dominance of the transformed clone over non-transformed hematopoietic progenitor cells.[7-9]

Table 1: *World Health Organization Classification of Myeloproliferative Neoplasms (MPN).*[10]

Chronic myeloid leukemia
Polycythemia vera
Essential thrombocythemia
Primary Myelofibrosis
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia/not otherwise categorized
Hypereosinophilic syndrome
Mast cell disease
MPNs, unclassifiable.[10]

This classification scheme, of course, implies that we know more about these disorders than we actually do. In fact, among hematologic disorders – particularly malignant ones – PV, IMF, and ET are among the least well understood with reference to research in our region.[10]

A common theme of aberrant activation of tyrosine kinase signaling pathways has emerged among the myeloproliferative neoplasms. Not only has this helped further our understanding of these complex disorders, but also identification of aberrant kinase signaling cascades has led to targeted small molecule inhibitors, such as imatinib, being used successfully in the treatment of certain diseases. Thus, the diagnosis and classification of the MPNs and overlap disorders requires correlation of morphology with clinical, hematologic, and molecular genetic findings. In categorizing these disorders the MPNs, there are the four common disorders, recognized as chronic myelogenous leukemia (CML), with its characteristic 9;22 translocation and BCR/ABL fusion protein,[11] and three non-CML MPDs: polycythemia vera (PV), essential thrombocythemia (ET), and chronic idiopathic myelofibrosis (CIMF). These common non-CML MPDs (PV, ET, CIMF) share a high incidence of the acquired point mutation (V617F) in the JAK2 kinase,[12] a cytoplasmic tyrosine kinase important in hematopoietic proliferation.

The MPNs also include a number of uncommon or atypical disorders. These uncommon MPDs include chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES), systemic mastocytosis (SM) with and without eosinophilia, chronic neutrophilic leukemia (CNL), MPN uclassifiable.[10]

Chronic myelogenous leukemia (CML) is the most common of the MPDs and can occur at any age. The average age at diagnosis is 50 to 60 years old with a slightly increased male-to-female ratio.[13]

PV appears to be more common in men than in women, with reported male-to-female ratios ranging from 1.2 to 2.2 in various studies. PV in younger patients reportedly shows less male predominance. Some but not all studies have suggested that the incidence of PV is increasing over time.[13]

PMF is a rare disease, with reported incidence figures that range from 0.4 to 1.5 per 100,000. Based on a large Mayo Clinic database of well-documented cases, median age at diagnosis was ~57 years, with a male to-female ratio of 1.6 (unpublished).[13]

ET is the most frequent among the MPDs, with an annual incidence that is estimated to be between 0.2 and 2.5/100,000 and point prevalence rates that exceed 10/100,000. It should be noted that true incidence rates are probably higher because most patients with ET are asymptomatic and thus unrecognized. In a cohort of 605 ET patients seen at the Mayo Clinic, median age at diagnosis was 57 years, and females represented 66% of the patient population.[8,13]

PATIENTS AND METHODS

This study was conducted from 4th April 2007 to 4th April 2013 at Haematology Department, Shaikh Zayed Hospital, Lahore. This was a cross-sectional descriptive study and included 200 cases. Patients aged 16 years and above, both sexes and diagnosed cases of CMPD were included. CBC and Bone marrow was done in all cases. Venous sample of 2 ml was collected from the antecubital vein by a 19 G needle after cleaning the skin by 70% alcohol. Blood film was fixed in methyl alcohol, stained by May-Grunwald-Giemsa stain and peripheral smear examination was done for red cell, leukocyte, platelet morphology and differential leukocyte count. Bone marrow aspirates were done by Islam Bone marrow aspirate needles® under local anesthesia observing an aseptic technique. The right iliac crest was chosen for all aspirates procedures. A volume of 3 ml bone marrow aspirates was collected and 12 – 15 bone marrow aspirate films were made fixed, stained by May – Grunwald – Giemsa staining technique and morphological examination was done. The collected data was entered into SPSS-15 for analysis.

RESULTS

In this study, we categorized 200 cases into 4 groups. There were 136 (68%) cases of CML, 20 (10%) of PV, 16 (8%) of ET and 28 (14%) of IMF (Table 1). In 136 cases of CML, mean age of patients were 40 years with maximum number of patients in 4th decade of life. PRV in 20 cases, mean age was 64 years and maximum number of patients in 7th decade of life. In 16 cases of ET mean age was 70 years with maximum number of patients in 7th decade of life. 28 cases of IMF having mean age 55 years with maximum number of patients in 6th decade of life (Table 2). Analysis of gender distribution shows that there were 80 (58.8%) males and 56

(41.2%) females (male to female ratio was 1.4:1) in CML. Eight males (40%n) and 12 females (60%) (with male to female ratio was 1:1.5)in PRV. In ET 16 males (100%) respectively. In IMF 12 males (42.8%) and 16 females (57.2%) with male to female ratio was 1:1.3 (Table 3).

Table 2: *Frequency and percentage of subtype of chronic myeloproliferative disorders [CMPD] (n = 50).*

Type of CMPD	*No.*	*%*
Chronic myeloid leukemia	136	68.0
Polycythemia rubra vera	20	10.0
Essential thromyocythemia	16	8.0
Idiopathic myelofibrosis	28	14.0

Table 3: *Frequency and percentage of chronic myeloproliferative disorders according to age.*

Age (Years)	*Chronic Myeloid Leukemia (n=136)*		*Polycythemia Rubra Vera (n = 20)*		*Essential Thromyocythemia (n = 16)*		*Idiopathic Myelofibrosis (n = 28)*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
16 – 20	12	8.8	-	-	-	-	4	14.2
21 – 30	28	20.5	-	-	-	-	4	14.2
31 – 40	40	29.4	-	-	-	-	-	-
41 – 50	32	23.5	-	-	-	-	-	-
51 – 60	-	-	4	20.0	-	-	16	57.4
61 – 70	8	5.8	16	80.0	12	75.0	4	14.2
71 – 80	16	11.7	-	-	4	25.0	-	-
Mean ± SD	40 ± 13.7		64.0 ± 5.1		70.0 ± 9.1		55 ± 22	

Table 4: *Frequency and percentage of chronic myeloproliferative disorders according to sex.*

Sex	*Chronic Myeloid Leukemia (n = 136)*		*Polycythemia Rubra Vera (n = 20)*		*Essential Thromyocythemia (n = 16)*		*Idiopathic Myelofibrosis (n = 28)*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Male	80	58.8	8	40.0	16	100.0	12	42.8
Female	56	41.2	12	60.0	-	-	16	57.2
Male: Female ratio	1.4:1		1:1.5		-		1:1.3	

DISCUSSION

The study comprised of 200 cases of which CML was found to be most common and ET was the least common disorders diagnosed. There were 136 cases of CML, most of these cases were diagnosed in 4th decade of life. In a study done by Sawyerl[14] peak incidence was found in 3rd and 4th decade. In a local study by Sayed et al[15] and in an Indian study by Deshmukh et al[16] found peak incidences were again noted in 3rd and 4th decade of life. Mean age of patient in CML cohort was 40 years. Kavasnicka et al[17] reported mean age was 50 years. In our study, there were 20 (10%) cases of PV. Mean age was 64 years with peak incidence in 7th decade. In a study by Spivak et al[18] in America it was 65 years while in a local study by Usman et al[19] mean age was 51.3 years. The results of the present study are also comparable with other studies. There were 16 cases of ET in our study. In these cases mean age was 70 years (range 62 – 83 years). In study done by Chim et al[20] it was 65 years while in a study by Thiele et al[21] it was 56 years. Majority of our patients presented in 7th decade of life. In a study by Chim et al[20] it was seen that 59% of patients were in 7th decade at the time of diagnosis. In patients of IMF, mean age was 55 years and peak incidence in 6th decade. Visani et al[22] and Clark et al[23] reported mean age of 60 years in American populat-

ions.

In our study, there was a male predominance. Males were 58.8% and females were 41.2 of total number of CML cases. Similar studies by Savage et al[14] and Kvasnicka et al[17] also reported male predominance i.e. 58% and 57.5% respectively. Male to female ratio in the present study, CML was 1.4:1 showed a male predominance like this study. Male to female ratio was 1:1.5 in PV in our study. All other studies have reported a male predominance, Chim et al[24] reported it as 1.1:1 and Usman et al[19] reported it as 4.5:1. This discrepancy can be explained by racial difference and environmental factors. In our study all the patients of ET were males. Equal male to female ratio was reported in studies by Steven et al[18] and Chim et al.[20] In the present study, there were 12 males (42.8%) and 16 females (57.2%) in IMF. Cervantes et al[25] reported identical gender distribution in their study in 1997 while in 1998 in a larger cohort[25], they noticed an increase (62%) in female patients. Our results are close to this study.

It is ***concluded*** that in CMPD, Chronic Myeloid Leukemia is commonest and Essential Thrombocythemia was least common. Demographic features of CML showed mean age of 40 years with peak incidence in 3rd and 4th decade and there was male preponderance. In IMF, mean age was 55years with male preponderance and peak incidence was in 6th and 7th decade. In cases of PRV, mean age was 65 years. Female preponderance was noted in our study which was not seen in other studies. ET was least common with mean age of 70 years. All cases were male.

Authors' Contribution

TA: Data collection, data interpretation, results and references. MA: Discussion writing and proof reading of article.

ACKNOWLEDGEMENTS

All praises to Allah Almighty.

REFERENCES

1. Tefferi A, Elliott M, Pardanani A. Atypical myeloproliferative disorders: diagnosis and management. Mayo Clin Proc. 2006 April; 81 (4): 553-563.
2. Dameshek W. Some speculations on the myeloproliferative syndromes. Blood. 1951; Apr; 6 (4): 372-375.
3. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood, 2016 Jan. 1: Blood – 2016.
4. Tefferi A, Gilliland DG. The JAK2V617F tyrosine kinase mutation in myeloproliferative disorders: status report and immediate implications for disease classification and diagnosis. Mayo Clin Proc. 2005; 80: 947-958.
5. Kralevics RS, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005 April 28; 352 (17): 1779-90.
6. Adamson JW, Fialkow PJ, Murphy S, Prchal JF, Steinmann L. Polycythemia vera: stem-cell and probable clonal origin of the disease. N Engl J Med. 1976 Oct. 21; 295 (17): 913-6.
7. Adamson JW, Singer JW, Catalano P, Murphy S, Lin N, Steinmann L, Ernst C, Fialkow PJ. Polycythemia vera: further in vitro studies of hematopoietic regulation. J Clin Invest. 1980; 66 (6): 1363.
8. Prchal JF, Axelrad AA. Letter: bone-marrow responses in polycythemia vera. N Engl J Med. 1974; 290 (24): 1382.
9. Swolin B, Weinfeld A, Westin J. A prospective long-term cytogenetic study in polycythemia vera in relation to treatment and clinical course. Blood, 1988; 72: 386-395.
10. Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood 2007; 110 (4): 1092–1097.
11. Gotlib J, Maxson JE, George TI and Tyner JW The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. Blood 2013; 122 (10): 1707–1711.
12. Reilly JT, McMullin MF, Beer PA, Butt N, Conneally E, Duncombe A, Green AR, Michaeel NG, Gilleece MH, Hall GW, Knapper S. Guideline for the diagnosis and management of myelofibrosis. British journal of haematology, 2012; 158 (4): 453-71.
13. Geotge IT. Pathology of Myeloproliferative disorders .ln: Greer JP, Rogers GM , Foerster J, Paraskeva F, Luken SJ, Glader B , Editors . Wintrobe's Clinical haematology 13" ed. Phladelphia: Lipincott Williams & Wilkins; 2015: 1980-2047.
14. Sawyers CL. Chronic Myeloid Leukemia. N Engi J Med. 1999; 340 (17): 1330-1340.
15. Sayed NN Usman M, Khaliq G, Adil SN, Khurshid M. Clinico-pathologic features of Chronic Myeloid Leukemia and risk stratification according to Sokal score. J Col Physicians Surg Pak. 2006; 16 (5): 336-339.
16. Deshmukh C, Saikia T, Bakshi A, Amare-Kadam P, Baisanc C, Parikh P. Imitinab mesylate in Chronic Myeloid Leukemia: a prospective, single arm, non randomized stud. J Assoc Physicians Ind. 2005; 53: 291-295.
17. Kvasnicka HM, Thiele J, Schmitt-Graeff A, Diehl V, Zankovich R, Niederle N, et al. Bone marrow features improve prognostic efficiency in multivariate risk classification of chronic phase Ph1+ chronic myelogenous leukemia: a multicenter trial. J Clin Oncol. 2001; 19 (12): 2994-3009.
18. Spivak JL, Diagnosis of the myeloproliferative disorders: resolving phenotypic mimicry. Semin Hematol 2003; Jan; 40 (1 suppl. 1): 1-5.
19. Usman M, Bilwani F, Kakepoto GN, Adil SN, Sajid R, Khurshid M, Polycythemia Vera and Idiopathic erythrocytosis and laboratory parameters comparison of clinical and laboratory parameters. J pak Med Assoc 2004 May; 54 (5): 249-251.
20. Chim C, Kwong Y, Lie AK, Ma S, Chan C, Wong L, et al. Long term outcome of 231 patients with essential thrombocythemia. Arch Intern Med. 2005 Dec: 165 (22); 12-26.
21. Steven S. Essential thrombocythemia: A review of dia-

gnostic and pathologic features. Arch Pathol Lab Med. 2006; 130 (80): 1144-1150.
22. Vasani G, Finally C, Castelli U, Peti MC, Ricci N, Vianelli L. Myelofibrosis with myeloid metaplasia: clinical and haematological parameters predicting survival in a series of 133 patients, B J Hematol. 1990; 75 (1): 4-9.
23. Clark DA, Williams WL. Myelofibrosis in: Foerster J, Luken SJ, Paraskeva F, Geer JP, Rogers GM, Editors. Wintrobe's clinical hematology. 12th edition. Philadelphia: Lippincott William's & Walkins, Company; 2015: 2274.
24. Chim C, Kwong PT, iang R. Polycythemia in Chinese patients: Thirty Six years of experience. Am J hematol. 2001; 66 (4): 274-279.
25. Cervantes F, Pereira A, Esteve J, Monsterrat R, Frances C, Rozman C, et al. Identification of short lived and long lived patients at presentation of Idiopathic myelofibrosis. B J Hematol. 1997; 97: 335-340.