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Presentations in Patients of Chronic Myeloid Leukemia; an Observational Study Focusing On the Association of Haematological Parameter on Gender

Amna Masood Bhutto[1*], Ahsan Ali Siddiqui[2], ZarghoonaWajid[3], Aisha Moin[4], Amsa Khan[5], Maham Rizvi[6], Anas Bin Tariq[7], Summaiya Iqbal[8], Muhammad Asim Khan[9] and Adnan Anwar[10]

[1]Resident Medical Oncology, Oncology Ward, Jinnah hospital, Pakistan

[2]Public Health, Specialist Family Medicine, Ministry of Health, Riyadh, Pakistan

[3]M Assistant, Musavvir Stem cell Clinic and Pathology Laboratory, Pakistan

[4]House Officer, Jinnah Postgraduate Medical Center, Pakistan

[5]House Officer Jinnah Postgraduate Medical Center, Pakistan

[6]Senior Medical officer, Community Health Services, Pakistan

[7]House Officer, Altibri Medical College and hospital, Karachi, Pakistan

[8]Hamdard College of Medicine and Dentistry, Hamdard University Hospital, Pakistan

[9]Medical officer, Ziauddin Medical University, Pakistan

[10]Assistant Professor, Al Tibri Medical College Karachi, Pakistan

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***Corresponding author:** Amna Masood Bhutto, Resident Medical Oncology, Oncology Ward, Jinnah hospital, Pakistan, E-mail: amnam12@gmail.com*

Abstract

Objective: The aim of this study was to evaluate association of haematological parameters on gender basis in chronic myeloid leukemia patients admitted in medical oncology department of the Jinnah Postgraduate Medical Centre, Karachi, Pakistan.

Material and methods: This was a cross sectional observational study through convenient sampling technique which was conducted from April 2016 to September 2017 in Oncology ward of Jinnah Postgraduate Medical Centre, Karachi after ethical approval. The total of 98 patients who were admitted in haematology oncology unit diagnosed as CML on complete blood picture and marrow examination, aged >18 years were incorporated in the study. Incomplete data and the patients who did not give informed consent were excluded from the study. Patients were divided into two groups on the basis of gender. Group 1 comprised of male patients (n=46) and Group 2 of female patients (n=52). SPSS version 20.0 was used for data analysis and Mann Whitney test was applied to assess the significance set at the level of <0.05.

Results: A total of 98 patients with 46 males and 52 females were included in the study having mean age of 40.24±11.63 and 40.48±13.60 respectively. The mean±SD and median of variables was recorded in these two groups. Haemoglobin level (gm/dl) was 9.32±2.26 and 9.20 in males while in females was 9.94±9.53 and 8.45 (p=0.158), total leukocyte count (x10^3 cells/mm^3) was 232.10±166.88 and 205.50 in males while 227.46±142.67 and 223.50 x10^3cells/mm^3 in females (p=0.884), platelets (x10^3cells/mm^3) in males was 455.14±354 and 361.5 though in females was 484±261.60 and 481.50 (p=0.222). However myelocyte count (%) in males and females was 13.87±7.49 and 12.50 whilst 18.65±7.49 and 18.0 respectively.

Conclusion: The present study predicted that considerable difference did not exist in various hematological parameters of male and female CML patients. However, there was significant difference observed in myelocyte count of these patients on the basis of gender.

Key Words: Chronic Myeloid Leukemia; Gender Basis;

Introduction

Leukemia has the highest mortalities of any malignancy [1]. Out of all leukemias, 15-20% are Chronic myeloid leukemia (CML) [2]. Chronic Myeloid Leukaemia (CML) is malignancy of blood that arise from a molecular alteration in a solitary pluripotent haematopoietic stem cells resulting in continuous production of the myeloid progeny [3]. In 90% of cases, CML is caused due to the existence of Philadelphia chromosome and infrequently by Hyperdiploidy of greater than 50 chromosomes [4]. The translocation among chromosome 9 and 22 t (9,22) (q34;q11) leads to the development of break point cluster region and Abelson's (BCR-ABL) a new fusion genes that codes for an oncoprotein (P210) positioned in the cytoplasm that has a strong ability to activate tyrosine kinase which as a result

activates numerous signals that convert hematopoietic stem cells into the leukemic cells, consequently augmented tyrosine kinase action which plays a vital role in the pathogenesis of CML [5]. In spite of leukemia induced factors, there are risk factors that augment the CML and these factors comprise of low socio-economic class, occupational contact to benzene, formaldehyde, elevated doses of ionizing radiation amongst the atomic bomb survivors, other risk factor such as alcohol misuse, obesity, weight gain throughout adulthood and effects of preservatives or pesticides used in the food industry can also cause CML [6,7]. Clinically CML are asymptomatic in 50 percent of cases while remaining patients presented with anemia, splenomegaly, fever, bleeding predisposition, hepatomegaly, lymphadenopathy and complications such as renal failure, hearing loss and priapism. Laboratory results include complete blood count, peripheral blood and bone marrow examinations revealing decreased hemoglobin, total white blood cell count(WBC) between 287×10^9./L and 535.7×10^9./L, thrombocytopenia or normal platelet count or thrombocytosis and peripheral blood smear primarily including amplified number of mature and immature granulocytes [8,9]. The current developments in the authentication of diagnosis of CML by sensitive tests such as qualitative real time-polymerase chain reaction (RT-**PCR**) to recognize transcript variants of BCR-ABL fusion genes and quantitative droplet digital PCR as well as RT-PCR tests are used for ratio of BCR- ABL transcripts values with usual genes on the international scale (>1016 and to monitor the patients response to therapy with chronic myeloid leukemia) [10,11]. The noticeable improvements in the management of CML with first line gold standard therapy of imatinib mesylate (IM), the first tyrosine kinase inhibitor (TKI), targets the BCR-ABL1 oncoprotein which causes leukemia, the second line therapy of TKI such as nilotinib and desatinib and allogenic bone marrow transplantation are used in case of failure of three TKI in chronic phase and 3rd line therapy includes management of accelerated phase and blast phase requires extended use of TKI and allogenic bone marrow transplant [12]. BCR- ABL–positive cells are hereditarily unbalanced and are prone to build up multiple and heterogeneous genomic alterations such as point mutations greater than 90 in the kinase domain (KD) that leads to conversion of the leukemic phenotype from chronic to acute hence resulting in resistance to the tyrosine kinase inhibitors [13]. One of the studies compared the effectiveness and safety of dasatinib with imatinib in patients with recently diagnosed chronic myeloid leukemia (CML) in chronic phase (CP). Preliminary outcome revealed that dasatinib had met its principal end point of advanced efficiency compared with imatinib and had an adequate safety profile, that lead to its approval for first-line use [14].

In numerous studies, it was predicted that dasatinib constantly exhibited deep and rapid responses. The progression-free survival (PFS) and overall survival (OS) remained elevated and comparable between dasatinib and imatinib. Additionally, the safety profile of dasatinib was steady through each update [15-18].

The objective of this study was to determine the hematological levels of patients diagnosed with CML on gender basis. Furthermore it was also aimed to assess the association of hematological parameters in male and female patients.

Methodology

Cross sectional observational study through convenient sampling technique was conducted for interval of one and half year from April 2016 to September 2017 in Oncology ward of Jinnah Postgraduate Medical Centre (JPMC), Karachi. Ethical approval was taken from the Institutional review board of JPMC, Karachi.

Ninety eight patients (98) admitted in haematology oncology unit divided into two groups were elected for the study. Group 1 comprised of male patients (n=46) and Group 2 of female patients (n=52). All CML patients recently diagnosed on complete blood picture and marrow examination, aged >18 years, were incorporated. Any case of CML who previously received chemotherapy and patients not willing to participate or having deficiency in diagnostic criteria were excluded from the study. Informed consent was taken from the patients with absolute concealment of the data. Demographic data which included age and gender was documented. Complete blood picture was performed in pathological laboratory of Jinnah Hospital, which included haemoglobin, total leukocyte count, haematocrit, mean corpuscular volume, neutrophils, reticulocytes, basophils, eosinophil, lymphocytes, promyelocytes, myelocytes, metamyelocytes, blast cells, platelets and plasma cells. Patients were divided into two groups on the basis of their gender.

For data analysis the statistical software SPSS version 20.0 was used. The quantitative data was expressed as mean, standard deviation, median and inter-quartile range (IQR). Shapiro Wilk test was used to verify the normal distribution. Mann-Whitney test was applied to evaluate the significance at 0.05 levels.

Results

In total of 98 CML patients included in this study with 46 males (group1) and 52 females (group 2) the mean age was 40.24±11.63 and 40.48±13.60 respectively. The mean and median (IQR) of various haematological parameters was reported in comparison to males and females. Mean±SD and median (IQR) of haemoglobin levels were 9.32±2.26 and 9.20 (7.75-10.92) g/dl in males while 9.94±9.53 and 8.45(7.30-9.67) g/dl in females. The hematocrit (%) was 33.63±4.56 and 33.15(30.15-36.50) in males though 32.15±3.81 and 32(30.35-34.0) in females. MCV was found to be 90.76±10.61 fl and 91.50(83-100)fl in group 1 whilst 91.53±13.09 fl and 94.50(81-100) fl in group 2. TLC in males was 232.10±166.88 and 205.50(95.46-329.75) $x10^3$ cells/ mm^3 while 227.46±142.67 and 223.50(125.96-324.35) $x10^3$ cells/ mm^3 in females. In males neutrophils (%) were 58.67±12.65 and 62(52.75-69.0) though in females were 53.09±16.75 and 56(45.0-62.75). Reticulocytes (%) were 5.33±12.30 and 2.70(2.10-3.13) in males whereas .31±0.89 and 2.40(1.55-2.98) in females. Basophils (%) were reported as 3.78±2.27 and 3.50(2.0-6.0) in group 1 whereas 4.42±2.79 and 5.0(2.0-6.0) in group 2. Eosinophils (%) 2.93±1.41 and 3.0(2.0-4.0) in males while 3.12±1.58 and 3.0(2.0-4.0) in females were seen in our

study. However lymphocytes (%) in males were 7.84±16.0 and 3(2.0-7.0) though 5.97±7.18 and 3(2.0-6.38) in females. Mean and median (IQR) for promyelocytes (%) was 5.24±3.34 and 5(3.0-7.0) in males whilst 4.46±3.98 and 3(2.0-5.0) in females. Myelocytes (%) in group 1 were 13.87±7.49 and 12.50(8.0-18.50) whilst in group 2 were 18.65±7.49 and 18.0(13.0-22.0). In males monocytes (%) were 3.06±2.09 and 2.75(1.50-4.0) though in group were 2.81±1.39 and 3(2.0-4.0). Metamyelocytes (%) in males were 9.41±5.35 and 9(5.75-12.0) while in females were 8.89±6.13 and 7(5.0-11.0). In group 1 blastocytes (%) were 3.02±1.27 and 3(2.0-4.0) whereas in group 2 were 4.0±3.13 and 3(2.0-5.0). Platelets ($x10^3$ cells/ mm^3) in males were 455.14±354 and 361.5(231.2-558.7) though in females were 484±261.60 and 481.50(289.25-627.75). Plasma cells (%) were 3.22±1.60 and 3(2.0-5.0) in males while 3.44±1.39 and 3(3.0-5.0) in females (Table 1).

Table: 1 Descriptive analysis of haematological parameters in different groups (n=98)

Variables	Group 1 (n=46)		Group 2 (n=52)	
	Median(IQR)	Mean±SD	Median(IQR)	Mean±SD
Hemoglobin (gm/dl)	9.20(7.75-10.92)	9.32±2.26	8.45(7.30-9.67)	9.94±9.53
Hematocrit (%)	33.15(30.15-36.50)	33.63±4.56	32(30.35-34.0)	32.15±3.81
MCV (fl)	91.50(83-100)	90.76±10.61	94.50(81-100)	91.53±13.09
TLC ($x10^3$cells/mm^3)	205.50(95.46-329.75)	232.10±166.88	223.50(125.96-324.35)	227.46±142.67
Neutrophils (%)	62 (52.75-69.0)	58.67±12.65	56(45-62.75)	53.09±16.75
Reticulocytes (%)	2.70(2.10-3.13)	5.33±12.30	2.40(1.55-2.98)	2.31±0.89
Basophil (%)	3.50(2.0-6.0)	3.78±2.27	5.0(2.0-6.0)	4.42±2.79
Eosinophil (%)	3.0 (2.0-4.0)	2.93±1.41	3.0(2.0-4.0)	3.12±1.58
Lymphocytes (%)	3.0 (2.0-7.0)	7.84±16.0	3.0(2.0-6.38)	5.97±7.18
Promyelocytes (%)	5.0 (3.0-7.0)	5.24±3.34	3.0(2.0-5.0)	4.46±3.98
Myelocytes (%)	12.50(8.0-18.50)	13.87±7.49	18.0(13.0-22.0)	18.65±7.49
Monocytes (%)	2.75(1.50-4.0)	3.06±2.09	3.0(2.0-4.0)	2.81±1.39
Metamyelocytes (%)	9.0(5.75-12.0)	9.41±5.35	7.0(5.0-11.0)	8.89±6.13
Blast cells (%)	3.0(2.0-4.0)	3.02±1.27	3.0(2.0-5.0)	4.0±3.13
Platelets($x10^3$cells/mm^3)	361.5(231.2-558.7)	455.14±354	481.50(289.25-627.75)	484±261.60
Plasma cells (%)	3.0(2.0-5.0)	3.22±1.60	3.0(3.0-5.0)	3.44±1.39

Table: 2 Association of haematological parameters with different groups

Variable	Groups				p-value
	Group 1(n=46)		Group 2 (n=52)		
	Mean Rank	Sum of Ranks	Mean Rank	Sum of Ranks	
Hemoglobin	53.82	2475.50	45.68	2375.50	0.158
Hematocrit	54.54	2509	45.04	2342	0.098
Mean corpuscular volume	48.13	2214	50.71	2637	0.654
Total leucocyte count	49.05	2256.50	49.89	2594.50	0.884
Neutrophils	55.29	2543.50	44.38	2307.50	0.058
Reticulocytes	53.95	2481.50	45.57	2369.50	0.145
Basophil	46.24	2127	52.38	2724	0.280
Eosinophil	48.43	2228	50.44	2623	0.724
Lymphocytes	47.58	2188.50	51.20	2662.50	0.525
Promyelocytes	55.20	2539	44.46	2312	0.060
Myelocytes	39.99	1839.50	57.91	3011.50	0.002
Monocytes	49.79	2290.50	49.24	2560.50	0.922
Metamyelocytes	52.30	2406	47.02	2445	0.357
Blast cells	47.12	2167.50	51.61	2683.50	0.425
Platelets	45.77	2105.50	52.80	2745.50	0.222
Plasma	47.14	2168.50	51.59	2682.50	0.418

The mean rank was also recorded in comparison to male and female patients of CML. Mean rank of hemoglobin was 53.80 in males whereas 45.68 in females (p-value=0.158). Hematocrit was 54.54 in males while 45.04 in females (p-value=0.098). MCV was seen to be 48.13 in males whilst 50.71 in females (p-value=0.654). TLC was 49.05 in group 1 though 49.89 in group 2(p-value=0.884). In males neutrophils were 55.29 while in females were 44.38 (p-value=0.058). Reticulocytes were 53.95 in males though 45.57 in females (p-value=0.145) .Basophils were 46.24 in males while 52.38 in females (p-value=0.280). Eosinophil in group 1 were 48.43 though in group 2 were 50.44 (p-value=0.724). Lymphocytes were 47.58 in males while 51.20 in females (p-value=0.525). Promyelocytes in males were noticed to be 55.20 while 44.46 in females (p-value=0.060). Myelocytes were 39.99 in males whilst 57.91 in females (p-value=0.002). In males monocytes were 49.79 though in females were 49.24 (p-value=0.922). Metamyelocytes in group 1 were seen to be 52.30 while 47.02 in group 2 (p-value=0.357). Mean rank of blast cells were 47.12 in males while 51.61 in females (p-value=0.425). Platelets were 45.77 in males though 52.80 in females (p-value=0.222). Plasma cells in males was 47.14 whilst in females was 51.59 (p-value=0.418) (Table 2).

Discussion

This study is one of its own kinds in the way that the gender-related haematological variations in chronic myeloid leukemia (CML) patients have not been conducted in previous studies. Study done by berger U et al., in 2005 reported that female patients were elder at diagnosis than male patients (51 vs 46 years; P<0.0001). Also females presented with lower hemoglobin (11.7 vs 12.5 g/dl; P<0.0001) and elevated platelet counts (459 vs 355 × 10^9/l; P<0.0001) however no differences were observed in WBC counts, bone marrow blasts, promyelocytes, basophils and eosinophils.[19] According to another study conducted by Lee JP et al., on considerably larger proportion (p = 0.019) of females compared to males presented with extensively low hemoglobin (<12 g/dL) and MCV values for women were appreciably (p = 0.02) lower than those for men, suggestive of the presence of iron-deficiency anemia as a possible contributing factor. Additionally, a notably greater proportion (p = 0.041) of females compared to males present with drastic elevation in platelet counts (>450 × 10^9/L). In fact, we suspect that the chief contributing factor to females presenting with lower hemoglobin and elevated platelet counts is iron deficiency. However in this study, iron studies were missing in the majority of patient records, but when using mean corpuscular volume, a substitute for iron status, it was seen that women present with appreciably lower MCV comparable to men. Proportional differences for white blood cell count data were not noteworthy [20]. These three characteristics (low haemoglobin, low MCV and elevated platelet count) were recognized in earlier studies as chief adverse pre-treatment prognostic factors. [21,22,23] These findings mentioned in above studies are inconsistent with our results in which no significant differences were seen in any of the haematological parameters among males and females except for myelocytes (p-value=0.002). A study was conducted in Nigeria with 16 female and 18 male CML patients. All the patients had leucocytosis (mean 287 X 10^9/L, range 72-1343 X 10^9/L) on presentation. No case of thrombocytopenia was reported, but nine (26.5%) patients with a mean platelet count of 639.1 X 10^9/L had thrombocytosis [24].

The quantitative approach of our study has assured that we have assessed the extensive range of patients with chronic myeloid leukemia. Nevertheless, the study might not be immune from observer bias. Considering the views of our study and to what range the hematological parameters are consistent with the other demographic variables would be revealing to discover more facts about the disease.

Conclusion

The present study predicted that considerable difference did not exist in various hematological parameters of male and female CML patients. However, there was significant difference observed in myelocyte count of these patients on the basis of gender.

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