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ORIGINAL ARTICLE

Clinical, hematological and cytogenetic analysis of Chronic Myelomonocytic Leukemia in Pakistan: A single-center cross-sectional study.

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ABSTRACT… Objective: The study was done to outline clinical, hematological, and cytogenetic profile of chronic myelomonocytic Leukemia (CMML) in Pakistani population. **Study Design:** Cross Sectional study. **Setting:** National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD), Karachi, Pakistan. **Period:** January 2022- December 2023. **Methods:** All baseline investigations and clinical parameters of CMML patients were recorded. Bone marrow biopsy samples were taken and cytogenetic analysis was performed. Descriptive statistics were reported by using SPSS version 25.0. Association between two categorical variables was evaluated using Chi-square test and Fisher exact test. **Results:** A total of 29 patients were included in the study having median age 62 (5-85) years with male predominance (62.1%). The most common presenting complaint was lethargy in 29 (100%) patients, followed by weight loss in 22 (75.9%) and fever in 21 (72.4%). The median hemoglobin levels were 9.3 (ranging 5.4-14.2) g/dL, total leucocytes count (TLC) 39.4(ranging 3.4-145.8x10^9/L and absolute monocyte count (AMC) of 5.5 (ranging1.14-61.54) x10^9/L. Twenty-two (75.9%) patients had normal karyotype and 04(13.8%) had an abnormal karyotype. There was no statistical difference in patient outcomes in decitabine users and non-users. **Conclusion:** This was one of the first studies conducted on CMML Pakistani patients. The clinical and hematological demographics were similar to those reported by international studies. Further clinical follow up and treatment analysis would be important addition to the existing data done prospectively. Future longitudinal studies with inferential statistics are needed in this context at national level.

Key words: Chronic Myelomonocytic Leukemia, CMML, Clinical-hematological Characteristics, Cytogenetics, Decitabine, Treatment.

INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic disorder with overlap features of myeloproliferative and myelodysplastic syndromes(MPN/MDS) having characteristic peripheral monocytosis with absolute monocyte count (AMC) >1 x10□/L and relative >10% of the white blood cells (WBCs).[1] CMML is a rare entity compared to other MPN/MDS with a strong preponderance in elderly men (median age 70 years at the time of diagnosis) and poor survival outcomes with median survival of 11 to 25 months.[2] CMML is reported as 0.35 cases per 100,000 American population and 0.46 per 100,000 in a study from southeast England.[3,4] Overall, several studies from various western countries have reported incidence of CMML as 1-4 cases per million each year.[5-7] There are limited studies on CMML in Asian countries and few studies have been reported from China, India, Korea, and Hong Kong.[5,8-11] A comprehensive study on CMML characteristics has not been published in Pakistan; with only one case of childhood JMML reported from Pakistan.[12]

The World Health Organization (WHO) 5th edition updated the diagnostic criteria of CMML in 2022. The prerequisite criteria included persistent peripheral blood monocytosis [absolute monocyte count >0.5 (x10□/L) and relative >10% of the (WBC), blast count of less than 20% in peripheral blood (PB) and/or bone marrow (BM), and not

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meeting criteria for other myeloproliferative neoplasms including chronic myeloid leukemia and myeloid/lymphoid neoplasms with tyrosine kinase fusion.[13] The presence of myeloid lineage dysplasia, acquired clonal cytogenetic or molecular abnormalities or defective partitioning of monocytes subsets are other supportive criteria. When the peripheral monocytes are >0.5 but <1 x10^9/L (after exclusion of other causes), 2 supportive criteria must be met for diagnosis. The sub grouping was based on the blast counts in the PM and BM. CMML-1 classified as <5% blasts in PB and <10% blasts in BM and CMML-2 comprises 5-19% blasts in PB and 10-19% in BM.[13]

CMML has diverse clinical heterogeneity and high propensity to transform into frank leukemia in about 15-30% of the patients.[14] The pathogenesis of the disorder is complex and multiple molecular pathways are implicated in its development, but no single pathway or cytogenetics is specific for the disease.[15] The literature reports about 20 to 30% CMML patients having clonal cytogenetic abnormalities; the most common being trisomy 8, loss of chromosome Y, monosomy 7, deletion 7q, deletion 20q, trisomy 21, and derivative 3q.[16]

The CMML patients are divided into different groups via multiple prognostic scoring systems but the efficacy of predicting outcomes via these scores remains variable. The CMML prognostic scoring system (CPSS) is most frequently used to stratify risk based on red cell transfusion dependence, total leucocytes count, blast percentage and cytogenetics.[17] Newer systems (CPSS-mol and Mayo molecular scores) utilize molecular abnormalities (ASXL1, NRAS, RUNX1, SETBP1) to improve the predictability of prognosis.[18]

CMML poses a diagnostic and therapeutic challenge to the hemato-oncologist because of its rarity, heterogeneity, requirement of exhaustive and expensive investigations to exclude other disorders and limited data on treatment options.[14] There is no single finding on BM histopathology that is pathognomonic of CMML, and the diagnosis is based on evaluating multiple parameters; commonly reported histopathological findings are granulocyte proliferation with dysplasia and monocytosis. The immunohistochemistry is often necessary to identify monocytes and its precursors.[14]

In a third-world country like Pakistan, managing patients with CMML becomes even more precarious due to financial restraints and unpredictable responses to standard therapy. Unavailability of chemotherapeutic agents is another factor that compromises patient care. These challenges are aggravated by the lack of promising studies on CMML in Asian patient demographic except for few studies.[8-11] This study presents real-world data highlighting the clinical, hematological and cytogenetic profile of Pakistani CMML patients diagnosed at single hematological referral center.

METHODS

This prospective cross-sectional study was conducted at National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD), Karachi, Pakistan from January 2022 to July 2023. Approval of the institute's research ethics committee was taken before starting the study with IRB no: NIBD/IRB-225/29-2021. The online open Epi sample size software was used for the calculation of sample size. The calculated sample size was 29. A total of twenty-nine CMML patients were included in the current study. All the patients who were diagnosed with CMML during the study period were included in the study on the basis of the 2016 WHO classification. Patients with reactive monocytosis, acute myeloid leukemia (AML), chronic myeloid leukemia (CML) with BCR-ABL1 fusion gene, Polycythemia vera (PV), primary Myelofibrosis and essential Thrombocythemia (ET) were excluded from the study. The clinical data was collected by obtaining detailed history, physical examination and signs of the disease recorded on patient's first visit to the hematology clinic. Participation of the patients in this study was voluntary, and written informed consent was taken.

Blood samples were collected from peripheral venous source and analyzed by Sysmex XN-1000

analyzer (Sysmex Corporation, Kobe, Japan) for complete blood count (CBC). Bone marrow samples were collected from the posterior superior iliac crest under local anesthesia with the Jamshidi needle. These samples were stained with Leishman's stain to delineate histology of the hematopoietic cells in the specimen. Standard protocol was used to perform cytogenetic analysis on bone marrow cultures that were stimulated for 72 hours, overnight, and 24 hours without stimulation. Using the International System for Human Cytogenetic Nomenclature (ISCN) 2013, the karyotypes was described using the GTG (G-bands via trypsin utilizing Giemsa) banding technique, and the Meta system was then utilized to create the karyograms. Fluorescence in situ hybridization (FISH) was used to detect known abnormalities as quality control for karyotyping. The Prognostic classification was done according to the CMML-specific prognostic scoring system (CPSS).[17] For definitive treatment, allogeneic stem cell transplantation (allo-HSCT) was offered to all the eligible patients. The patients who were ineligible for allo HSCT on the basis of factors like poor performance status, comorbidities or frailty or had limited financial resources to afford transplant were offered hypomethylating agents (HMA) i.e. Azacitidine and decitabine, cytoreductive therapy and best supportive care including blood product transfusion and prophylaxis antimicrobials.

Statistical Analysis

Data was collected by using MS Excel and analysis was done by using statistical package for the social sciences version 25.0 (SPSS Inc, Chicago, IL, USA). Normality of data was assessed by applying Shapiro Wilk test and it was not normally distributed. Descriptive statistics were reported in values of mean and median; ranges were computed for quantitative variables and percentages for categorical variables. Association between two categorical variables was calculated by using Chi-square test and Fisher exact test and a p-value of <0.05 was considered to be significant. The overall survival analysis was estimated by Kaplan Meier.

RESULTS

In total, 29 patients with CMML were included in the study. The male to female ratio was 1.6:1 with a median age of 62 years (ranging from 25-85 years). Demographic, hematological and bone marrow findings of all the patients are summarized in Table-I

Variables	Baseline distribution in cohort n=29
Age (years), median (range)	62 (25-85)
Male gender, n (%)	18 (62)
Splenomegaly, n (%)	19 (65.5)
Hepatomegaly, n (%)	11 (37.9)
Lymphadenopathy, n (%)	03 (10.3)
Co-morbid illness	**N (%)**
Diabetes mellitus	06 (20.6)
Hypertension	04 (13.7)
Ischemic heart disease	01 (3.4)
Hypothyroidism,	01 (3.4)
CBC parameters	**Median (range)**
Hb (g/dL)	9.3 (5.4-14.2)
HCT (%)	30 (16-42)
WBC ($x10^9$/L)	39.4 (3.4-145.8)
ANC ($x10^9$/L)	14.4 (0.27-76.2)
AMC ($x10^9$/L)	5.5 (1.14-61.54)
Platelets (10^9/L)	58 (2-746)
Peripheral Blasts (%)	04 (1-13)
BM Blasts (%)	06 (1-19)
Lineage of marrow dysplasia	**n (%)**
Erythroid Dysplasia	14 (48.3)
Myeloid Dysplasia	26 (89.7%)
Megakaryocytic Dysplasia	12 (41.4%)
WHO classification 2016	**n (%)**
CMML-0	12 (41.4)
CMML-1	07 (24.1)
CMML-2	10 (34.5)

Table-I. Demographics, hematological and BM findings of CMML patients:

Hb: Hemoglobin, HCT: Hematocrit, WBC: White leucocytes counts, ANC: Absolute Neutrophils Counts, AMC: Absolute Monocyte counts, n: Number of patients, BM: Bone marrow, CMML: Chronic Myelomonocytic Leukemia

About 22 (75.9%) patients had normal cytogenetics and 04 (13.8%) patients had abnormal karyotypes i.e. monosomy 7 in 02 patients, trisomy 21and trisomy 08 in the other 02 patients. Three patients

had culture failure hence cytogenetics was not reportable. (Figure-1)

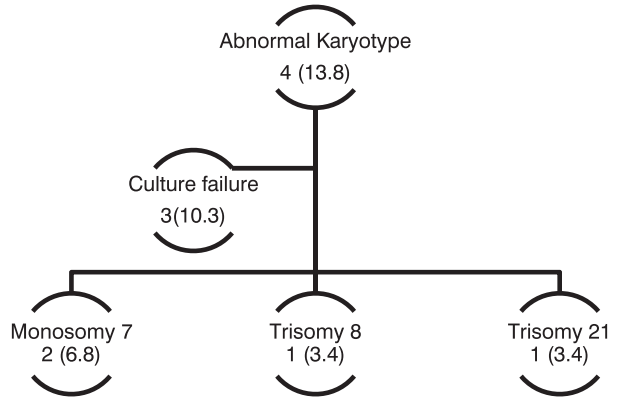

Figure-1. Frequency of cytogenetics abnormalities in CMML patients.

On clinical evaluation, the most common presenting complaint was lethargy in 29 (100%) patients, followed by weight loss in 22 (75.9%) and fever in 21 (72.4%), splenomegaly in 19 (65.5%), hepatomegaly in 11 (37.9%) patients, and 03 (10.3%) were found to have adenopathy. Eight (27.5%) patients presented with a history of recurrent infections. Amongst these, urinary tract infection, pneumonia and sepsis were common. All patients with visceromegaly and adenopathy had high WBC counts (>13x10^9/L). Ten (34.4%) patients had known co-morbid which are highlighted in Table-I. The CPSS scoring of the patients is represented in Figure-2.

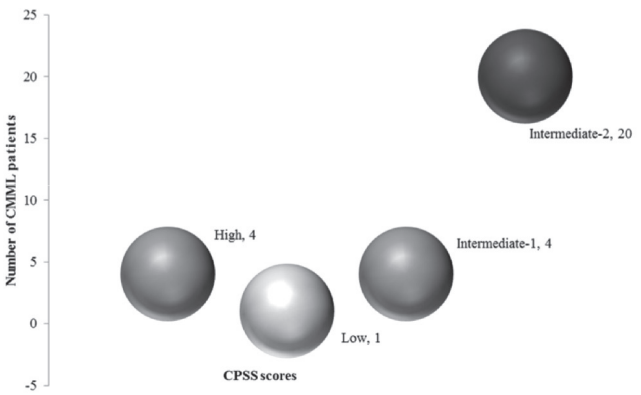

Figure-2. CPSS scoring of CMML patients.

Transfusion dependence was defined as an average of more than 02 units of blood transfused every 28 days over 03 months, and it was prevalent in our cohort, as 18 (62.1%) patients were transfusion-dependent. Treatment was offered to all patients except 03, out of them 02 were lost to follow after diagnosis and one died immediately after diagnosis due to sepsis. Management included HMAs (Azacitidine and Decitabine), the FDA approved disease modifying agents for transplant ineligible patients in CMML, cytoreductive treatment with hydroxycarbamide (HC) and Cytarabine, and best supportive care measures treatment with blood transfusion and prophylactic antimicrobials. (Table-II) Allo HSCT which is one of the curative treatment in CMML was offered to eligible patients but was deferred by patients due to severe financial constraints.

Treatment Administered	n (%)
Hydroxycarbamide	06 (20.6)
Hydroxycarbamide + Decitabine	10 (34.4)
Hydroxycarbamide + Cytarabine	04 (13.7)
Hydroxycarbamide + Cytarabine + Decitabine	04 (13.7)
Azacitidine	02 (6.89)
Untreated	03 (10.3)

Table-II. Details of treatment administered to CMML patients:

Thirteen (44.8%) patients were transformed to acute myeloid leukemia (AML).Treatment outcomes of decitabine use in association with disease-related patient variables like transfusion dependence, recurrent infections, transformation to AML and death are presented in Table-III.

Variables		Decitabine (n)		P-Value
		Not Received	Received	
Transfusion dependence	No	04	07	0.264
	Yes	11	07	
Recurrent infections	No	12	08	0.245
	Yes	03	06	
Transformation to AML	No	10	07	0.096
Yes		05	07	
Alive	No	07	07	0.689
	Yes	4	07	

Table-III. Association of decitabine used with variables in CMML patients:
n= Number of patients out of 29

Out of 29 CMML patients, only 11 were alive at

the end of the study, while 11 had died and 7 were lost to follow-up. The median follow-up time for the study was 3 months. The survival function of the patients is presented in figure 03, showing an overall median survival of 13 months.

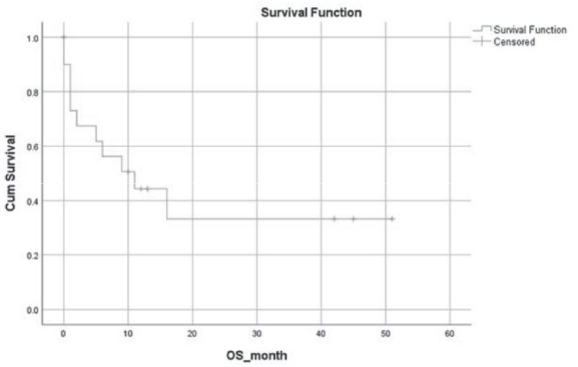

Figure-3. Survival analysis of CMML patients.

DISCUSSION

CMML is a rare hematological malignancy having overlap characteristics of MDS and MPN (depending on WBC count and marrow dysplasia) with persistent monocytosis.[19] This study presented clinicohematological and cytogenetic profile of CMML from a dedicated hematology healthcare center in Pakistan. Considering the rarity of the disorder, a cohort of 29 patients was analyzed to highlight the baseline characteristics of CMML, correlate certain patient variables with decitabine use and report survival analysis of the cohort.

The median age of diagnosis was 62 years (ranging from 25-85 years), which was similar to the studies of Ma L, et al. and Wang C, et al.[5,8] and dissimilar with Korean and American studies as they have observed higher median age at the time of diagnosis (more than 70 years at the time of diagnosis) as the overall age was same, ranging in between 60 to 80 years.[3,9] The male preponderance reported globally was also observed in the current cohort as 18 (62%) patients were men with approximate male to female ratio of 1.6:1, similar to the studies from China, Korea, Hong Kong, America, and Barcelona.[5,8,10,20]

The clinical presentation of the patients was with constitutional symptoms such as lethargy, followed by weight loss and fever.[21] Initial clinical features depicted stark similarity to Chinese, Indian, and Italian population of CMML patients with predominant splenomegaly.[5,11,20] Majority of patients (86.2%) had high WBC count (>13 x10□/L) similar to aforementioned studies.[5,9,11,22,23] Proliferative subtype was common in our study, as seen in Asian and American population; however, Castaño-Díez S, et al. reported predominant dysplastic subtype (CMML-MD 67.9% and CMML-MP 32.1%) in Barcelona population.[20]

In hematological parameters, the median value of WBC counts was 39.4(x10□/L) with one patient having counts as high as 145.88(x10□/L) with monocyte counts of 14.5 (x10□/L). This is divergent from previously mentioned Asian studies as they report overall WBC count of less than 20(x10□/L).(5, 9, 11, 20, 22) Bone marrow dysplasia was more common in myeloid lineage 26 (89.6%), from these about 6 (20.6%) patients had dysplasia in all three lineages.

Cytogenetic analysis was performed in all 29 CMML patients; 22 (75.86%) had normal karyotype, abnormal cytogenetics was found in 04 patients (monosomy 7, trisomy 8 and trisomy 21) which was similar to the commonly reported cytogenetics of CMML and 03 patients had culture failure.[12,14] Interestingly, all the patients with abnormal karyotype had myeloproliferative type of CMML (WBC >13 x10□/L). One patient with monosomy 7 transformed to AML despite monthly decitabine cycles and the other patient with monosomy 7 was lost to follow. The patient with trisomy 21 was also lost to follow up thus his disease course could not be evaluated. The patient with trisomy 8 transformed to AML and died on subsequent follow-up.

Treatment of CMML comprises supportive care consisting of blood component transfusion and cytoreduction; while disease modifying treatment is comprised of HMA (decitabine and azacitidine) with or without allogeneic bone marrow transplantation which is the definitive treatment approach with curative potential.[15,19] Cytoreductive therapy is required in patients with high WBC counts before or in combination with HMA.[15,19] The predominant proliferative

subtype in the studied CMML patients warranted cytoreductive therapy, i.e. cytarabine and/ or hydroxyurea. Patients were treated with hydroxyurea, combination of hydroxyurea and cytarabine, decitabine and azacitidine. Three (10.3%) patients did not receive any treatment because 02 (6.89%) were lost to follow after diagnosis and one died due to sepsis.

In the current study, 18 (62%) CMML patients were transfusion dependent (packed red cells). Similarly, PIAZA study from Germany and a Polish study reported blood component transfusion dependence in their CMML patient cohort that was 40% and 59.3% respectively.[24,25] In the present study, 16 (55.1%) CMML patients treated with hydroxyurea required blood transfusion, the remaining one patient was on azacitidine and one was not on any cytoreductive therapy or HMA due to CMML complicated by sepsis. In comparison, Wang C, et al. reported that out of their 66 CMML patients, 13 (19.6%) were given hydroxyurea with blood transfusion and 14 (21.2%) required transfusion alone.[8] None of the patient could be preceded for allogeneic stem cell transplant (SCT).

There was no statistically significant difference in outcomes between patients who did or did not receive decitabine (Table-III). This could be because majority of patients who received decitabine were given less than 6 cycles due to either logistical issues (financial constraints, unavailability of drugs, patient preference) or clinical problems (neutropenic sepsis). Santini V et al, reported that longer survival was observed in high-risk CMML patients who responded after 6 cycles of decitabine as compared to non-responders.[22] Infections remained the predominant cause of death in patients who received HMA, while disease-related complications led to poor outcomes in patients who did not receive HMA. The overall median survival was found to be 13 months and it demonstrated similarity with internationally reported survival.[2-6]

There are potential challenges in treating CMML in our healthcare set-up. First is the non-affordability or unavailability of drugs at times when patients need them, second is the low literacy rates of the patients that resulted in lost to follow-up or refusal of treatment and finally, the suboptimal outcomes of standard therapy (HMA) which brought about a sense of hesitancy and futility in choosing these treatment options. Rezazadeh A, et al. recently outlined proposals for clinical trials in CMML and emphasized on better treatment options given HMA induced complete remission in less than 20% of patients and did not prolong survival compared to hydroxyurea.[26] A latest phase 3 clinical trial conducted within the European Myelodysplastic Neoplasms Cooperative Group (EMSCO) network reported that decitabine did not improve event-free survival (EFS) in comparison to hydroxyurea in 171 patients with advanced proliferative CMML randomized to receive either of the drugs.[27]

The major patient subset (41%) in the current study were labeled as CMML-0 with marrow blasts less than 5 % yet, 13 (44.8%) patients transformed to acute leukemia and 05 (17.2%) died during 24-months follow-up. Unfortunately, 07 (24.1%) patients were lost to follow- up and their current status was not known, so the death ratio might be higher than what was reported. The likely etiology of loss of contact with patients was low literacy rates, financial collapse and deterioration of patient's mental health. These issues are prevalent in our country and this led to a more complicated course of the disease, highlighted by the fact that only 04 (13.7%) patients were still on ongoing treatment and proper follow-up. This calls for the development of more practical and holistic methods to approach CMML in third-world countries like Pakistan. Our study had certain limitations like small sample size and single center representation. Additionally, the genetic testing was not performed in patients as it was very expensive and done at very limited centers in Pakistan outsourcing the testing internationally. Moreover, we at our center were in the initial phase of validation and quality control (QC) of next generation sequencing (NGS). Nevertheless CMML is a rare disorder and to the best of our knowledge, this was the first detailed cross-sectional study that reported baseline characteristics of CMML in Pakistani population

and compared the findings with international studies, with an intention to better understand the heterogeneous disease and for developing more effective and economical treatment options. In future multicenter prospective collaborative studies with larger sample size are needed for better representation of national data. Moreover, the incorporation of molecular testing will also give better inference on disease prognosis and upfront treatment with allo HSCT for high risk patients.

CONCLUSION

CMML is a rare, heterogeneous hematological malignancy of the elderly and its pathogenesis and efficacious treatment options are still being explored. In the current study it was observed that the clinical, hematological and cytogenetic profile of CMML in Pakistani patients were similar to the previously reported studies. In depth, analysis for significant variations with larger sample size is needed across the different hematological centers in Pakistan.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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2	**Aisha Arshad:** manuscript writing,
3	**Naveena Fatima:** Statistical analysis and collection of patient's data.
4	**Laraib Majeed:** Statistical analysis.
5	**Nida Anwar:** Conception of the study, designed, edited, critically reviewed and approved the final version of the manuscript.