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Research Article

Hematological, clinical, cytogenetic and molecular profiles of confirmed chronic myeloid leukemia patients at presentation at a regional cancer centre of North-Eastern India: a cross-sectional study.

Manasi Bhowmik[1], Subrata Bhowmik[2], Prasun Bhattacharjee[3].

[1]Medical Officer, Medical Oncologist, ABV RCC, Agartala, Tripura, India.
[2] Assistant Professor, Department of Medicine, Agartala Government Medical College, Agartala, Tripura, India.
[3]Consultant Physician, Department of Medicine, North Tripura District Hospital, Dharmanagar, Tripura, India.
Corresponding Author: Dr Subrata Bhowmik.

Abstract

Background: The evidence on hematological, clinical, cytogenetic and molecular profiles among new CML patients are very insufficient in the developing countries like India and more so in the North-eastern states.. Therefore, this study is performed among newly confirmed CML patients at Atal Bihari Vajpayee Regional Cancer Center (ABV RCC), Agaratala, Tripura.
Objective: To determine the hematological, clinical, cytogenetic and molecular profiles of confirmed CML patients at a regional cancer centre of North-Eastern India.

Methods: A hospital-based cross-sectional study was conducted to evaluate hematological, clinical, cytogenetic and molecular profiles of confirmed CML patients at ABV RCC from January 2024 to December 2024. A structured questionnaire was used to collect the patients' sociodemographic information, medical history and physical examination, and blood samples were also collected for hematological, cytogenetic and molecular tests. Descriptive statistics were used to analyze the sociodemographic, hematological, clinical, cytogenetic and molecular profiles of the study participants.

Results : A total of 76 confirmed new CML patients were recruited for the study. The majority of patients were male, 151 [60.2%]; chronic (CP) CML, 213 [84.7%]; and had a median age of 37 years. The median (IQR) WBC, RBC and PLT counts were 216.8 (154.02–306.2) $x10^3/\mu L$, 3.3 (2.74–3.7) $x10^6/\mu L$, and 328 (209–502) x $10^3/\mu L$, respectively. All patients had leukocytosis and 94.73%, 92.7% and 99.2% of the patients developed anemia, hyperleukocytosis and neutrophilia, respectively. Fatigue, abdominal pain, splenomegaly and weight loss were the common signs and symptoms observed among CML patients. Approximately 97.3% of the study participants were Philadelphia chromosome positive (Ph+) . P210, the major breakpoint protein, transcript was detected by both qualitative polymerase chain reaction (PCR) and quantitative real time polymerase chain reaction (PCR).
Conclusion : Most CML patients were presented with hyperleukocytosis, neutrophilia and anemia. Fatigue, abdominal pain, splenomegaly and weight loss were the most common signs and symptoms observed in the CML patients. The majority of CML patients arrive at referral center with advanced signs and symptoms, so strengthening of peripheral health resources to facilitate early recognition of the condition is of utmost importance .

Keywords: CML,BCR ABL, Hyperleukocytosis

Introduction

Chronic myelogenous leukemia, also known as Chronic myeloid leukemia (CML) is a hematopoietic stem cell (HSC)-derived myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. It is caused by chromosomal translocation (9; 22). CML accounts for 20% of all leukemias affecting adults.The formation of the Philadelphia (Ph) chromosome and the expression of the breakpoint cluster region (BCR)-Abelson murine leukemia viral oncogene homolog 1 (ABL) fusion gene result from the fusion of a portion of the BCR on chromosome 22 with the ABL tyrosine kinase on chromosome 9 [1, 2].

CML is manifested by anemia, thrombocytosis, and left-shifted leukocytosis [6]. Most cases of CML can be diagnosed using peripheral blood findings combined with molecular genetic techniques that detect t(9; 22) (q34.1; q11.2) or, more specifically, BCR::ABL1. To ensure sufficient material for a complete karyotype and for morphologic evaluation to confirm the disease phase a bone marrow aspirate is often required [7]. Patients in the chronic phase (CP) of CML have less than 10% blasts in their bone marrow samples [8]. The accelerated phase (AP) of CML is distinguished by bone marrow samples containing 10–20% blasts. The CML blast crisis (BC) phase has the same picture as acute leukemia; this stage contains more than 20% blasts, and large clusters of blasts are observed in the bone marrow and spread to tissues and organs other than the bone marrow [8, 9].

Molecular tests such as PCR and FISH for t(9;22) (q34;q11.2), which demonstrate BCR-ABLs, are essential for the diagnosis and confirmation of CML [10, 11]. The goals of treatment for chronic phase CML are to avoid progression to other advanced stages and to avoid adverse events (AEs) to restore and maintain quality of life so that patients can achieve a life expectancy comparable with that of the general population [12].

Hydroxyurea (HU) is an S-phase agent that acts by inhibiting DNA synthesis. This drug acts as an inhibitor of ribonucleotide reductase and can lower blood counts within 1 to 2 days, especially if higher than standard doses are used [13]. Tyrosine kinase inhibitors (TKIs) are potent drugs that significantly improve long-term outcomes in patients with CML [14].

In developing countries like India, CML is more commonly diagnosed in the advanced stage and in the younger age group (39 years) [3]. Early diagnosis and treatment of CML are highly important for preventing and controlling CML as its diagnosis and treatment delay worsen the condition further [13]. Besides, in low-income countries there is insufficient evidence on hematological, clinical, cytogenetic and molecular profiles among new CML patients. Thus, the aim of this study was to determine the hematological, clinical, cytogenetic and molecular profiles of confirmed CML patients during their first presentation at a Regional Cancer Centre of Northeastern India.

Methodology

The study was conducted at ABV RCC, Agartala.

A cross-sectional study was conducted among confirmed chronic myeloid leukemia patients who were first diagnosed at TASH between January 2024 and December 2024.

INCLUSION CRITERIA

CML patients who were diagnosed and confirmed by BCR-ABL-1, FISH and RT–PCR as CML patients for the first time at ABV RCC.

EXCLUSION CRITERIA

1. Patients with suspected CML who were BCR-ABL, FISH and RT–PCR negative and confirmed to be CML negative;
2. Patients who did not voluntarily provide blood samples; and
3. Patients who were extremely ill and unable to provide consent and samples.

A convenient sampling technique was used for all the newly diagnosed patients enrolled during the study period. All CML patients diagnosed between January 2024 and December 2024 were included consecutively to determine the hematological, clinical, cytogenetic and molecular profiles. Accordingly, 76 CML patients were recruited for the study.

Sample collection and laboratory analysis

Blood samples with a volume of 5 mL were collected in an EDTA test tube from all study participants by a certified laboratory expert. The CBC was analysed by autoanalyser and manually by specialist pathologist.

For molecular profiles, one of the results used for confirming CML was the Xpert BCR-ABL Ultra test. In vitro diagnostic tests for the quantitation of BCR::ABL1 and ABL1 mRNA transcripts in peripheral blood specimens from patients diagnosed with t(9;22)-positive CML expressing the BCR-ABLl fusion transcripts type e13a2 and/or e14a2 have been performed. The test utilizes automated, quantitative, RT–qPCR, but it could not differentiate e13a2 from e14a2. The Xpert BCR-ABL Ultra test is intended to measure BCR::ABL1-to-ABL1% ratios on the International Scale (IS).

The other test used for the study was the FISH technique for the initial screening of CML patients via both bone marrow and peripheral blood. The RT–PCR results were also consistent with the results of other tests we used for the present study, and these results constitute the gold standard for diagnosing and monitoring BCR::ABL1 transcript mRNA in CML patients. All FISH, qualitative and quantitative RT–PCR were performed abroad in India for all patients.

The data collected were cleaned, checked for completeness and entered in Excel spreadsheet. The data were subsequently exported to the Statistical Package for Social

Sciences (SPSS) version 26. The data were analyzed using SPSS. Descriptive statistics were used to analyze the sociodemographic, hematological, clinical, cytogenetic and molecular profiles of the study participants. The distribution of the data was checked, and the median and IQR were used for non-normally distributed data.

Operational definitions

Anemia Haemoglobin value < 13 g/dl for males and < 12 g/dl for females are considered as anaemia. Severe anemia ≤ 7 g/dl, moderate anemia 7.01– 10 g/dl, mild anemia 10.01–12 g/dl for females and 10.01– 13 g/dl for males.

Basophilia when a basophil count > 300 cells/μL is found in blood.

Clinical profile Signs and symptoms of CML patients during presentation.

Confirmed new CML patient Xpert BCR-ABL Ultra or FISH- or RT–PCR-positive patients confirmed for the first time as CML patients at TASH hematology clinics.

Eosinophilia when the eosinophil count is > 500 cells/μL in blood.

Hyperleukocytosis was defined as a WBC greater than 100,000/μL found in blood.

Neutrophilia was defined as a higher neutrophil count (> 7.9 × 103/μL). Prechemotherapy naive if the patients never received HU treatment

Prechemotherapy treated Patients who had received HU treatment

Splenomegaly Spleen swelling of the categorized size; massive splenomegaly > 10 cm, moderate 4–9 cm and mild size of 1–3 cm.

Thrombocytopenia a PLT < 150 × 103 cells/μL found in blood.

Thrombocytosis a PLT > 450 × 103 cells/μL found in blood.

Results

Sociodemographic characteristics of the study participants

A total of 76 CML patients were diagnosed and included in the study. Among the total study participants, 37 and 39 were naïve and HU-treated, respectively. More than half (53.94%, 41) of the patients were males. The median age of the study participants was 37 (IQR (29–47) years, and more than 87% of the study participants were ≤ 60 years old. More than half of the patients were from rural and hilly area.

Hematological profile of the study participants

The median (IQR) WBC count was 216.8 (154.02–306.2) $\times 10^3/\mu L$, which was determined for patients who were both naïve and treated with HU during presentation. The median (IQR) WBC counts for patients who were naïve and treated with HU were 259.2 (185.6-350.3) × $10^3/\mu L$ and 187.7 (188.3-291.63) $\times 10^3/\mu l$, respectively, during presentation. For the absolute neutrophil count (ANC), the overall median (IQR) was 168.8 (110.3-262.4) $x10^3/\mu L$, whereas for patients naive and treated with HU, the median (IQR) was 199 (136.12–293.4) $x10^3/\mu L$ and 144.25 (96.2-240.66) $x10^3/\mu L$, respectively.

For RBC parameters, the median (IQR) value for RBC was 3.3 (2.74–3.7) $x10^6/\mu L$. The median (IQR) RBC counts for patients who were naïve to treatment and those treated with HU were 3.06(2.7–3.7) $\times 10^6/\mu L$ and 3.5 (2.82–3.75) $\times 10^6/\mu L$, respectively. With respect to the PLT, the median (IQR) value was 328 (209–502) $x10^3/\mu L$. The median (interquartilerange (IQR)) PLTs for patients naïve and treated with HU were 320 (208–449) $\times 10^3/\mu L$ and 323.5 (210-507.65) $\times 10^3/\mu L$, respectively. There were significant differences in hematological parameters, such as the WBC count ($P < 0.001$), HGB count ($P = 0.024$), and HCT count ($P = 0.024$), between naive and HU treated groups (Table 2).

Common hematological abnormalities among new CML patients

All patients had leukocytosis, and greater than 92.7% of the patients had hyperleukocytosis. Among the study participants, 72 (94.73%) CML patients developed anemia, and moderate anemia was common among 40 (52.63%) CML patients, followed by mild anemia 22 (28.94%) and severe anemia 10 (13.15%) during presentation. The percentages of CML patients with eosinophilia and basophilia were 96.5% and 88.5%, respectively. However, the medians (IQRs) for eosinophils and basophils were 2.3 (1.4–3.85)% and 1.1 (0.3–3.3)%, respectively, of the total WBC count (Table 3).

Distribution of common hematological abnormalities among patients in the CML phases

Among the 37 HUnaïve and 39 HUtreated CP CML patients, 95.05% had hyperleukocytosis. Most CP-phase WBCs fell in the range of 101–250 × $10^3/\mu L$, whereas 13.67% CP and 33.3% AP patients had ≥ 351 × $10^3/\mu L$ WBC counts. In the AP CML phase,95.7% patients had hyperleukocytosis, whereas all eight BC CML patients had hyperleukocytosis. Among the 37 HUnaïve and 39 HUtreated CP CML patients, 62.7% and 45.1% had moderate anemia, respectively. Among the phases, 89.2% and 90% of the CPs and APs, respectively, developed anemia, whereas only one BC CML patient treated with HU was free from anemia. Regarding the PLT, of the 37 HUnaïve and 39 HUtreated CP CML patients,58.9% and 56.7%

had normal PLTs, respectively. Furthermore, thrombocytopenia was observed in 12.7%, 10% and 50% patients in the CP, AP and BC CML phases, respectively. Thrombocytosis was observed in 29% patients with CP, 31.8%) with AP and one patient in the BC CML phase. For the neutrophilic distribution, except for one patient in the CP CML phase, there was neutrophilia in all phases of CML.

Clinical profile of the study participants

Among 76 study participants, 64 (84.21%) were at the CP stage, 09 (11.84%) were at the AP stage, and 3 (3.94%) were at the BC stage. The majority of CML patients were symptomatic at the time of presentation; the most common symptoms were fatigue (72; 94.73%), abdominal pain (69; 90.78%), splenomegaly (70; 92.1%) and weight loss (66; 86.84%) (Fig. 1). The prognostic risk scores of all the study participant were calculated (Table 4).

Splenomegaly is one of the main symptoms of patients. A massive, moderate or mild increase in spleen size was indicated. Among the 76 study participants who had splenomegaly, 61.7% had massive splenomegaly with a spleen size > 10 cm, 33.8% had moderate splenomegaly with a spleen size of 4–9 cm, and 4.5% had mild splenomegaly with a spleen size of 1–3 cm. Approximately 84% of CPs had splenomegaly, whereas only one AP and one BP CML patient were free from splenomegaly.

Cytogenetic and molecular profiles

All of the study participants were positive for the Philadelphia chromosome or BCR::ABL1, and the p210 BCR::ABL1 fusion transcript was detected. After cytogenetic analysis of 76 confirmed CML patients,74 (97.3%) were Philadelphia chromosome positive (Ph+), whereas in two patients Philadelphia was absent or negative. The median (IQR) number of Ph + cells per 100 cells was 95% (85–100%) among the study participants diagnosed. Among the Ph + cases, the distributions of CML phases were 84.21%, 11.84% and 3.94% for CP, AP and BC, respectively. Except for one AP patient, all the other Ph-negative patients were CP CML patients.

Discussion

CML is characterized by anemia, thrombocytosis, and leukocytosis with a shift to the left. Molecular tests such as PCR and FISH for t(9;22) (q34;q11.2), which demonstrate BCR-ABLs, are essential countries as a result we motivated to describe these profiles among CML patients during presentation.

The median age was 37 years, and more than 87% of the study participants were ≤ 60 years old. This finding is consistent with the study conducted by Mulu Fentie A et al., which reported a total of 27.2% of patients aged 31–40 years [15]. These findings are comparable with those of the studies conducted by Tadesse F et al., in which the median age was 33 years [3], and by Ngono AP et al., in which the mean age was 39.2 years [1]. This shows that younger populations were affected by CML. In this study, males (60.2%) were more affected by CML than females were, with a ratio of 1.5:1. This finding is also similar to that of a study conducted in Pakistan, in which the male-to-female ratio was 1.6:1 [16, 17].

Among 76 study participants, 64 (84.21%) were at the CP stage, 09 (11.84%) were at the AP stage, and 3 (3.94%) were at the BC stage. These findings are similar to those of Kumar S et al., who reported that 83% of CML-CP, 12% of AP, and 5% of AP patients were in the BC phase in India [19]. Furthermore, a study from India by Srinivas KG et al. reported comparable findings: CP (90.1%), AP (4.5%) and BC (5.4%) [20].

However, our findings were inconsistent with those of Ngono AP et al. in Cameroon, especially for CP-CML (66%) [1], and with those of Sinha R. et al. [21] in India. Sinha et al. reported that 28.1% of patients were in the AP phase, which is higher than our finding (12.1%). Similarly, there were fewer findings in the BC phase than in Cameron, 22.7% of which were reported by Ngono AP et al. and 7.8% by Sinha R et al. in India [1, 21]. This difference could be due to the difference in sample size since the sample sizes for both patients were much smaller than our sample size and because of the difference in duration of symptoms.

The median (IQR) WBC count was 216.8 (154.02–306.2) ×103/, and all patients had leucocytosis, whereas 96.05% had hyperleukocytosis. This finding is similar to that of the study conducted by Tadesse F et al., which revealed that all the patients had leukocytosis [3]. Similarly, in a study conducted in Iraq by Al-abady I et al., the mean WBC count was 153.7 × 109/L, ranging from 29 to 436 × 109/L. Furthermore, in a study performed in Tanzania by Henke O et al., the median WBC was 300.5 × 109/L (78–499 × 109/L) [22]. This finding was also consistent with those of studies conducted by Ngono AP et al., Kumar et al. and Wiyono et al. [1, 6, 19]. Leukocytosis is expected in CML patients, but as most of the study participants had hyperleukocytosis, this could make diagnosis difficult because the patients need to come to TASH frequently and be forced to take HU for a longer time as the WBC count decreases to the recommended number (20–30 × 109/L and clinical parameters also considered) to start chemotherapy. This could also explain why CML patients dropped out before starting chemotherapy (imatinib, a first generation TKI) in our study area.

. For the absolute neutrophil count (ANC), the overall median (IQR) was 168.8 (110.3-262.4) x103/µL, whereas for patients naive and treated with HU, the median (IQR) was 199 (136.12–293.4) x103/µL and 144.25 (96.2-240.66) x103/µL, respectively.

Our study showed that almost all (99.2%) of the participants had neutrophilia, which is in line with the results reported from Tanzania by Tebuka E et al. (ANC 179(± 123) K/ µL) [22]. In addition, our study revealed that 88.5% of the study participants had basophilia,

although the relative percentage median (IQR) was 1.1 (0.3–3.3)%, which is comparable with the findings of Al-abady et al. [18]. . Neutrophils are among the WBC components that are expected to increase in CML patients; as a result, neutrophilia was observed in almost all the study participants.

For Hgb, the median (IQR) value was 9.3 (8.2–11) g/ dl. The median (IQR) values for patients who were naïve to treatment and treated with HU were 8.9 (7.9–10.2) g/ dl and 9.75 (8.33–11.2) g/dl, respectively. Approximately for the diagnosis and confirmation of CML [10, 11]. However, the data related to hematological, clinical, cytogenetic and molecular profiles of CML patients is very limited in low-income

mild anemia which was comparable with study conducted by Tadesse F et al. that reported 96.7% of CML patients had anemia [3]. These findings are also similar to those of a study by Kumar S *et al., in which* 13% had severe anemia, 58.8% had moderate anemia and 28.2% had mild anemia [19], and those of Ngono AP et al., in which 86.4%, 61.4% and 5.3% had moderate, respectively [1]. Furthermore, a study conducted by Chang F et al. revealed that 95.1% of patients developed anemia and mild anemia (22.8%) and moderate anemia (46.9%), but these proportions differed for severe anemia (30.1%) [16]. The difference may be due to sample size, duration of symptoms and geographical location. As expected, the incidence of anemia was high, and moderate anemia was the dominant anemia among the study participants; this was also related to the clinical stage at which the patients came to our study site.

With respect to the PLT, the median (IQR) value was 328 (209–502) x103/µL. The median (interquartilerange (IQR)) PLTs for patients naïve and treated with HU were 320 (208–449) ×103/µL and 323.5 (210-507.65) ×103/µL, respectively. Approximately 22 (28,94%) and 10 (13.1%) patients had thrombocytosis and thrombocytopenia, respectively. These findings were consistent with those of the study conducted by Ngono AP et al., which reported that a normal PLT was found in 80 (60.6%) patients, 11 (8.3%) had thrombocytopenia, and 41 (31.1%) had thrombocytosis [1]. In addition, our findings were comparable with those of a study conducted by Tadesse et al., which revealed that 23.3% of the study participants had thrombocytosis [3], however, there is some variation, which could be due to sample size differences or variations since our sample size was larger than those in those studies. In addition, this was an indication of the variation in the PLT among CML patients, which could be normal in some cases but thrombocytosis in others.

The duration of symptoms in our study participants (median (IQR)) was 5 (2.25-12) months, with a range from 0 to 60 months. These results were comparable with the results reported from Tanzania by Tebuka E et al., in which the duration of symptoms was 15 (± 9) months, ranging from 0 to 48 months [23]. All CML patients in this study were symptomatic at the time of presentation, and the common complaint was fatigue (96.4%), followed by abdominal pain (92%), splenomegaly (89.2%), weight loss (88%) and abdominal swelling (80.5%). These findings are in line with the findings of studies conducted by Sultan S et al., Al-abady I et al. and Sinha R [17, 18, 21]. This percentage was greater than that in the study by *Srinivas KG et al.*., which revealed that the common presentations were fatigue (72; 94.73%), abdominal pain (69; 90.78%), splenomegaly (70; 92.1%) and weight loss (66; 86.84%). Another Indian study revealed that fullness in the abdomen was 66.6%, fever was 59%, and fatigue was 55.5% [19]; these findings can be attributed to differences in sample sizes among studies, environmental factors and durations of symptoms. The majority of CML patients were symptomatic at the time of presentation; the most common symptoms were

Splenomegaly (92.1%) presented in different categorical sizes in this study; 61.7% patients had massive splenomegaly, 33.8% developed moderate splenomegaly, and 4.5.% had mild splenomegaly. These findings are comparable with the study performed by Tadese F et al., whose overall range was 3–26 cm [3] since most of the findings in our study indicated moderate and massive splenomegaly. Additionally, the prevalence of splenomegaly was comparable to that in a study performed in Pakistan [17], in which the prevalence was 89.3%. Furthermore, these findings are consistent with those of a study from India [19], which reported incidences of 62%, 22.2% and 15.6% for massive, moderate and mild, respectively. The difference in moderate and mild symptoms may be due to the duration of symptoms among the study participants, and the sample size could be the reason since our sample size was larger than that of their study participants.

Conclusion

On presentation, most of the CML patients had hyperleukocytosis, neutrophilia or anemia. Patients in younger age groups with a median age of 37 years and more than 87% ≤ 60 years were affected by CML in Tripura. Fatigue, abdominal pain, splenomegaly and weight loss were the most common signs and symptoms observed in the CML patients. A locally established reference range for hematological and clinical parameters should be established considering age, sex, geographical location and other variables, as well as access to advanced laboratory facilities for early detection and monitoring of cytogenetic and molecular parameters of CML patients.

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