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Prognosis of RUNX1-RUNX1T1 Rearrangement in Newly Diagnosed Acute Myeloid Leukemia Patients

Halima Babar, Hamid Saeed Malik, Muhammad Umar, Zahra Tasleem

ABSTRACT

Objective: To compare the clinical-hematological (including laboratory and morphological) parameters of newly diagnosed AML patients with RUNX1-RUNX1T1 rearrangement before and after induction therapy.

Study Design and Setting: This is a cross-sectional study, Department of Hematology, Armed Forces Institute of Pathology (AFIP), Rawalpindi from December 2021 to December 2022.

Methodology: 64 newly diagnosed patients with de novo t (8;21) AML were included. The RUNX1-RUNX1T1 fusion gene was detected using real-time reverse transcriptase polymerase chain reaction (RT-PCR); while t(8;21) was identified through chromosomal/cytogenetic analysis. All the clinical parameters, laboratory variables, blast percentages, and morphological parameters of newly diagnosed AML RUNX1-RUNX1T1 patients were compared before and after therapy. AML induction regimen included the following drugs: cytarabine along daunorubicin. Assessment of these patients was carried out four weeks after induction therapy.

Results: The patients' mean age was 60 (ranging from 14 to 85 years), with 46 males and 18 females. Statistical significance was observed in TLC (p-value < 0.001), Hb (p= 0.001), and platelet count(p=0.001) levels. After treatment, the blast size in peripheral blood was reduced to zero and both Auer rods and abnormal granules were absent in bone marrow blasts of patients. The average percentage of eosinophilia decreased from 8.52±1.76 before treatment to 2.42±1.79 after treatment.

Conclusions: Our study concluded that the treatment approach(cytarabine along with daunorubicin or idarubicin) for patients with RUNX1-RUNX1T1 AML resulted in improved blood counts, reduced blast cells, Auer rods, and abnormal granules; with a higher rate of complete remission and a lower incidence of relapse.

Keywords: Acute myeloid leukemia, AML with t (8;21), Complete Remission, Prognosis, RUNX1-RUNX1T1

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INTRODUCTION:

Acute myeloid leukemia (AML) is characterized by malignant clonal proliferation of progenitor cells in conjunction with differentiation arrest. The annual occurrence of AML, adjusted for age, in the United States (US), is 4.3 cases per 100,000 individuals. The frequency of occurrence rises as individuals get older, with a typical age of diagnosis being 68 years.[1] Unusual development of myeloid cells leads to an elevated presence of immature malignant cells and a reduced number of fully developed red blood cells, platelets, and white blood cells. AML's clinical appearance upon diagnosis might range from an accidental finding on a routine blood test to a life-threatening condition requiring immediate attention. AML is distinguished by the following characteristics, in addition to general symptoms such as exhaustion and loss of appetite: Anemia causes exhaustion and weakness of breath when exerted; neutropenia causes recurring infections; and thrombocytopaenia causes a higher susceptibility to bruising and bleeding. Untreated AML often leads to bone marrow failure, resulting in life-threatening symptoms that manifest rapidly over a span of weeks or months.[2] Acute leukemia is diagnosed when the bone marrow or peripheral blood contains 20% or greater numbers of blasts.[3] AML classification shifted from morphology to genetic-based, WHO includes AML with recurrent genetic

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abnormalities indicating specific changes.[4] The most significant indicators of prognosis in acute myelogenous leukemia (AML) are cytogenetic and morphological characteristics which have been used in diagnosis and therapy, as well as in understanding their pathogenesis.[5]

Acute myeloid leukemia (AML) with t (8;21) (q22; q22.1), accounts for approximately 4% to 8% of all AML cases. According to the FAB classification, this particular subtype is linked to the M2 subtype. It tends to occur in younger individuals, exhibits a distinct immunophenotype, frequently expresses CD19, and shows various additional cytogenetic abnormalities such as loss of a sex chromosome, deletion of the 9th long arm of chromosome 9, trisomy 8, all of which collectively contribute to a favorable prognosis.[6] The t (8;21) (q22; q22.1) translocation is an oncogenic change that results in the formation of a new hybrid gene, RUNX1-RUNX1T1, formed on the altered chromosome 8. This translocation produces a merged gene combining the chromosome 21 RUNX1 gene with the chromosome 8 RUNX1T1 gene (also called ETO) gene.[7] This subtype of AML is found to have a higher expected rate of complete remission (CR) and is associated with a favorable long-term outcome and lower incidence of relapse. The European Leukemia Net (ELN) considers the translocation t(8;21) and the resulting RUNX1-RUNX1T1 gene fusion as a favorable subset in AML risk stratification in 2017.[8] Both RUNX1 and RUNX1T1 play a crucial role in a transcriptional complex responsible for regulating significant target genes implicated in hematopoiesis.[9] The AML1-ETO (RUNX1-RUNX1T1) fusion product alters the core binding factor transcription complex, affecting proliferation, cell differentiation, apoptosis, and self-renewal which results in the induction of leukemogenesis.[10]

The purpose of the study is to compare the clinical-hematological (including laboratory and morphological) parameters of diagnosed RUNX1-RUNX1T1 AML patients before and after therapy. Complete remission (CR) of each AML patient post-induction therapy was determined and taken into account. Thus, this study determined the prognosis of RUNX1-RUNX1T1 in the Pakistani population.

METHODOLOGY

This cross-sectional study was performed at the Armed Forces Institute of Pathology (AFIP), Rawalpindi from December 2021 to December 2022 after taking approval from the Institutional Review Board (IRB), vide reference number OA-239-2023 After a thorough literature search, we calculated a sample size of 64 via the WHO calculator, keeping the margin of error at 5%, a confidence level at 95%, and AML prevalence at 4.3%.[1] Sampling was done using a non-probability consecutive sampling technique.

Patients of all ages and both genders who were newly diagnosed with AML with RUNX1-RUNX1T1 gene rearrangement were included in this study. Patients with acute leukemias other than AML, patients of AML with other recurrent genetic abnormalities, and AML patients already undergoing therapy were excluded.

Written consent was obtained before enrolling all patients and their confidentiality was ensured at all levels. Approval of the institutional ethical committee was also procured before starting the project. In this study, 64 newly diagnosed patients with de novo t(8;21) AML were included. The RUNX1-RUNX1T1 fusion gene was detected using real-time reverse transcriptase polymerase chain reaction (RT-PCR), while t(8;21) was identified through chromosomal/cytogenetic analysis. All patients underwent evaluation at the time of diagnosis and following induction therapy i.e. after four weeks. Clinical parameters such as age, gender, and organomegaly (hepatomegaly, splenomegaly) were observed. EDTA anti-coagulated blood sample from each patient was analyzed using the Sysmex XN 3000 automated hematology analyzer to record laboratory variables, including total leucocyte count (TLC), hemoglobin (Hb), and platelet count. The normal ranges for laboratory variables included: TLC (4-10)×10^9/L, Hb (13-17)g/dL, and platelets (150-450)×10^9/L.

Additionally, a bone marrow aspirate sample was obtained and subjected to cytochemical staining to determine blast percentages and morphological parameters, such as blast size, Auer rods, abnormal granules, and eosinophilia. Cytogenetics and molecular evaluation were done after obtaining blood/bone marrow samples from each patient in our study, before starting induction treatment. Cytogenetics used the FISH (fluorescence in-situ hybridization) technique.

All the clinical parameters, laboratory variables (including blast percentages), and morphological parameters of newly diagnosed AML RUNX1-RUNX1T1 patients were compared before and after therapy. AML induction regimen includes the following drugs: cytarabine along with daunorubicin or idarubicin. CR (Complete Remission) criteria according to WHO comprises of Neutrophil count: $=1x10^9$/L, Platelet count: $=100x10^9$/L, <5% myeloblasts without Auer rods in peripheral blood, transfusion independence and no splenomegaly (or no extramedullary disease).

Collected data was processed through SPSS 24, using standard protocol analysis. Baseline variables were analyzed descriptively using frequencies and percentages for qualitative variables and mean with standard deviation for continuous variables like pre-treatment and after-treatment. Statistically significant differences before and after intervention were assessed using Paired sample t-tests for continuous variables. Post-stratification chi-square test was applied for qualitative variables taking p-value = 0.05 as significant to check for a potential association between variables and response.

RESULTS:

In this study, a total of 64 patients diagnosed with de novo t(8;21)/RUNX1-RUNX1T1 AML were carefully selected

for enrollment. The mean age of the patients was found to be 60.0 years, with a range of 14 to 85 years. Among these patients, 46 (71.9%) were male, while 18 (28.1%) were female, as shown in Figure 1. Prior to treatment, their mean total leukocyte count (TLC) was 12.53±6.51 (x109/L), hemoglobin (Hb) level was 9.08±1.82 g/dL, and platelet count was 86.25±12.46 (x109/L). After treatment, the study observed a significant improvement in the TLC count, as well as a rise in both Hb and platelet counts. The mean TLC count after treatment was 8.06±2.04 (x109/L), Hb level was 11.03±1.48g/dL, and platelet count was 154.98±19.93 (x109/L). These improvements were statistically significant, with a p-value of less than 0.001 for TLC, and a p-value of 0.001 for both Hb and platelet count, as shown in Table I. This data provides valuable insights into the effectiveness of the treatment for de novo t(8;21)/RUNX1-RUNX1T1 AML, which can help improve patient care and outcomes.

Before treatment, larger-sized blasts (mean= 24.03±3.94%) were observed both in the peripheral blood and bone marrow. While after treatment, the blast count in peripheral blood and bone marrow was zero and <5%, respectively; a reduction in blast size was (mean: 3.35±1.05%) was also observed. Before treatment, Auer rods in myeloblasts were present in 98.4% of patients (n=63) and abnormal granules (also in myeloblasts) in 96.9% of patients (n=62). Following the induction therapy, it was observed that less than 5% of the circulating bone marrow myeloblasts contained Auer rods, indicating positive progress. Additionally, the percentage of abnormal granules in these blasts was significantly reduced, indicating an improvement in the condition. Prior to the induction therapy, the average percentage of eosinophilia was 8.52±1.76%. However, after the treatment, the percentage of eosinophilia reduced significantly to 2.42±1.79%, reflecting the effectiveness of the therapy. Table II presents a comparative analysis of the morphological characteristics of patients with AML with RUNX1-RUNX1T1 gene rearrangement before and after treatment. The analysis revealed a statistically significant difference between the morphological features of the patients before and after treatment, with a p-value of 0.001.

Figure 1: Distribution of patients according to gender

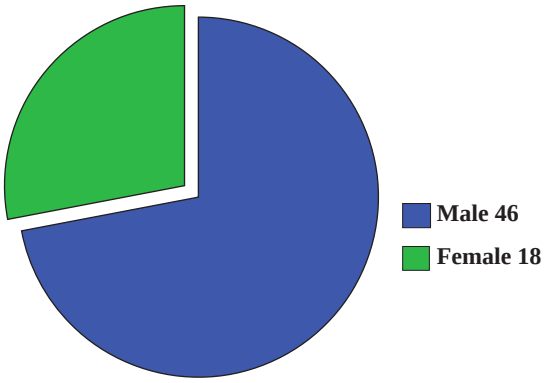

Table 1: Comparison of clinical and laboratory findings in AML with RUNX1-RUNX1T1 patients before and after treatment (n=64)

Parameters	Before	After	p-value
TLC ($x10^9$/L)	12.53±6.51	8.06±2.04	< 0.001
Hemoglobin (g/dL)	9.08±1.82	11.03±1.48	0.001
Platelet ($x10^9$/L)	86.25±12.46	154.98±19.93	0.001
Blast count (%)	50±30	3±2	0.001

Table 2: shows a statistically significant difference in morphological characteristics of newly diagnosed AML with RUNX1-RUNX1T1 patients before and after treatment (p-value of 0.001)

Parameters	Before Treatment	Before Treatment	p-value
Large blasts (%)	24.03±3.94	24.03±3.94	0.001
Auer rods (BM blasts)			
Present	63 (98.4%)	63 (98.4%)	0.001
Absent	1 (1.6%)	1 (1.6%)	
Abnormal granules			
Present	62 (96.9%)	62 (96.9%)	0.001
Absent	2 (3.1%)	2 (3.1%)	
Eosinophilia (%)	8.52±1.76	8.52±1.76	0.001

DISCUSSION:

AML is diagnosed by the presence of =20% blast cells of myeloid lineage in the peripheral blood and/or bone marrow.[11] Certain gene mutations are vital for managing the risk and clinical categorization of individuals with AML.[12] The chromosomal rearrangement t(8;21) is a well-acknowledged genetic abnormality in AML, that is usually observed in 5-12% of individuals with acute myeloid leukemia (AML) and is most commonly associated with AML with maturation (FAB type AML-M2).[13] According to recent studies, patients diagnosed with acute myeloid leukemia (AML) who have the RUNX1-RUNX1T1 rearrangement may benefit from intensive consolidation therapy as part of their treatment regimen. This type of therapy involves high doses of cytarabine, a medication that helps to destroy cancer cells. The studies suggest that patients with this particular genetic mutation who receive intensive consolidation therapy demonstrate improved rates of complete remission and long-term disease-free survival (DFS). These findings could have significant implications for the treatment of AML patients with the RUNX1-RUNX1T1 rearrangement, potentially leading to more effective and personalized treatment plans.[14-15] In classical t(8;21) AML patients, the utilization of anthracycline and cytarabine induction chemotherapy leads to remission rates reaching approximately 90%.[16-17]

Our study examined treatment response in 64 de novo t(8;21)/RUNX1-RUNX1T1 AML patients. Notably, male patients (46) outnumbered females (18) in the study. Pre-treatment blood parameters indicated compromised health. The mean Total Leukocyte Count (TLC) was 12.53±6.51 ($x10^9$/L), reflecting elevated white blood cell levels in the

majority of the patients taken in our research study. Hemoglobin (Hb) levels were below normal (mean: 9.08±1.82 g/dL) and platelet counts were also reduced (mean: 86.25±12.46 $x10^9$/L). After receiving treatment (cytarabine along with daunorubicin or idarubicin), positive changes were noted in the blood parameters/variables of the patients. There was a notable reduction in the TLC, with the average post-treatment TLC decreasing to 8.06±2.04 ($x10^9$/L). This decrease in TLC following therapy signifies a favorable treatment response and could potentially help relieve the burden of leukemia in the patients. Hb levels of patients rose significantly after treatment (mean: 11.03±1.48 g/dL). Platelet counts also increased notably (average: 154.98±19.93 $x10^9$/L). Morphological analysis showed promising results. Initially, the majority of the patients (98.4%) had Auer rods and abnormal granules (96.9%) found in the peripheral blood and bone marrow myeloblasts.

A 62-year-old woman was discussed in a case study by Lindsey *et al*,[17] When she was admitted to the hospital, her white blood cell count was 5 x 10^3/ìL with 17% blasts, her hemoglobin was 9.1 g/dL, and her platelet count was 22 × 10^3/ìL. The results of her bone marrow biopsy showed a significant population of blasts with round to irregular, intermediate-sized nuclei, prominent nucleoli, and scant to moderate cytoplasm; 59% blasts according to manual count. The translocation t(8;21) was detected in this patient using both conventional cytogenetics as well as FISH technique. The patient received conventional idarubicin and cytarabine treatment. The only complication was neutropenic fever, which had no identifiable infectious source. The treatment was successful as the patient achieved complete cytogenetic response (CCyR), maintaining this response for 18 months.

Another case of a 63-year-old female was also described by Lindsey *et al*,[17] The patient's WBC count was measured to be 6.1 × 10^3/ìL, with 67% of these cells being myeloblasts on peripheral blood examination. Additionally, her Hb level was 9.1 g/dL, and her platelet count was 4 × 10^3/ìL. A bone marrow biopsy revealed that the number of blasts had increased to 75% according to the estimated count. The patient was diagnosed as having AML with RUNX1-RUNX1T1 gene mutation (fusion detected on PCR). The patient received conventional idarubicin and cytarabine induction treatment, which helped her achieve a complete cytogenetic remission. Patients with the chromosomal rearrangement t(8;21), generally have a lower chance of experiencing a relapse.

Similarly, in their study, Kim *et al*,[18] found that Auer rods were present in 67% (14/21) of patients with AML-M2 in whom t(8;21) was found. The study also showed that blast cells with Auer rods and a high number of abnormal granules were more commonly observed in patients who tested positive for RUNX1-RUNX1T1 mutation. After treatment, Auer rods in <5% of bone marrow myeloblasts were nil and abnormal granules were scanty, indicating a positive cellular response. Our study showed that there was a significant decrease in eosinophilia following treatment. Following therapy, the percentage of myeloblasts in peripheral blood was reduced to zero and in bone marrow to <5%.

In a study conducted by the United Kingdom MRC, 5876 AML patients were analyzed, with 421 of them possessing the t(8;21) abnormality.[19] The results showed that this subset had a much better prognosis (p-value <0.001) and 61% long-term disease-free survival (DFS) rate, which is consistent with other studies.[20] In general, this study reveals that the therapeutic method is effective in treating de novo t(8;21) AML. The improvements in blood parameters, and morphological characteristics, including the reduction in blast count in both peripheral blood and bone marrow indicate a successful treatment outcome.

CONCLUSION:

In conclusion, this study offers valuable information on how patients with RUNX1-RUNX1T1 AML respond to therapy, with improvements in their blood counts. The treatment approach used resulted in significant rectification of TLC, Hb levels, and platelet count; as well as a reduction in blast cells, Auer rods, and abnormal granules. Moreover, the study indicates that the treatment approach has a higher rate of complete remission and a lower incidence of relapse. There are significant advances seen in terms of the treatment options available for AML patients since relapse is a common occurrence among these patients that can be challenging to manage.

Authors Contribution:
Halima Babar: Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
Hamid Saeed Malik: Data collection
Muhammad Umar: Data analysis
Zahra Tasleem: Literature search
Nazish Tahir: Data collection

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