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17p Deletion in Patients with De Novo Acute Myeloid Leukemia and their Clinico-Haematologic Features

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ABSTRACT

Objective: To determine the frequency of 17*p* deletion in patients with Acute Myeloid Leukemia and their clinical-hematologic features using fluorescence in situ hybridization.

Study Design: Cross-sectional study.

Place & Duration of Study: Department of Hematology, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Dec 2018 to Dec 2019.

Methodology: All diagnosed cases of Acute Myeloid Leukemia of all ages and genders were included. Interphase FISH testing was performed using blood or bone marrow specimens using 10µL of the Meta systems XL *p*53 probe, and a total of 500 nuclei per assay were analyzed using a fluorescent microscope. Del 17p positivity and negativity were noted. Clinico-haematologic features of the patients with and without del 17*p* were also noted.

Results: In our targeted population of 84 patients, there were 25(29.8%) females and 59(70.2%) males. The mean age of presentation was 36.3±1.6 years. The mean total leucocyte count(TLC)was 31.2±4.2×10^9/L, and the mean platelet count was 69.3±4.5×10^9/L. Del 17p was detected in a total of 8(9.5%) patients. The median age of patients with del 17p at diagnosis was 33 years, the mean TLC was 12.32±10.36x10^9/L, and the mean platelet count was 80±26.73*10^9/L. Prominent clinical features among patients with del 17*p* included fever and pallor.

Conclusion: Our study suggests a relatively low frequency of del 17*p* in AML (9.5%), which is consistent with international data.

Keywords: Acute myeloid leukemia, Clinico-haematologic features, Del 17p, Fluorescence in situ hybridization.

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INTRODUCTION

Acute Myeloid Leukemia is an aggressive haematological malignancy having an annual incidence of 3-4/100,000 individuals.[1] It is one of the most commonly occurring leukaemias in adults. Dyspnea, dizziness, weakness, fever and bleeding diathesis due to bone marrow failure are the main presenting features of AML.[2,3]

Acute myeloid leukaemia is a diverse genetic haematological disorder; half the cases carry clonal chromosomal abnormalities.[3] The acquired genetic changes in hematopoietic progenitors hinder normal cell growth and maturation mechanisms. Bone marrow blasts of most AML cases have at least one chromosome aberration at diagnosis time of diagnosis. Cytogenetics are considered the most valuable prognostic tool in anticipating remission rate, relapse and life expectancy.[4] Cytogenetic abnormalities with favourable prognosis are t(15:17), t(8;21) ,inv 16 and with poor prognosis are inv 3, t(6;9), monosomy 5, monosomy 7, complex karyotype, Philadelphia positivity and deletion 17p.[5] Increasing age, high TLC and response to induction therapy are some other important prognostic factors.[5]

17p deletion frequently involves the p53 gene on band 17p13.1.p53, a tumour suppressor gene whose function is to trigger cell-cycle arrest in reaction to genetic insults, oncogenes and hypoxia, followed by DNA repair.[6] Its down-regulation is a significant factor in tumour evolution in solid malignancies, and it has also been associated with disease advancement in haematological cancers. Loss of 17p frequently concurs with a complex aberrant karyotype, which has an inferior outcome.[7]

The fluorescence in situ hybridization(FISH) technique is a genetic technique that employs fluorescently labelled oligonucleotide probes for hybridization to specific DNA sequences.[8,9] Though conventional metaphase karyotyping can detect a wide range

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of cytogenetic aberrations, FISH presumably has a greater sensitivity for detecting a number of these abnormalities, importantly deletion of 17p (del 17p). In this study, we inspected the frequency, clinical and haematological features of 17p deletion in 84 patients with AML using the FISH technique.

METHODOLOGY

The cross-sectional study was conducted at the Department of Haematology Armed Forces Institute of Pathology (AFIP), Rawalpindi Pakistan, from December 2018 to December 2019 after the approval from the Ethical Committee (FC-HEM17-21/READ-IRB/18/665). We calculated the sample size using the WHO sample size calculator, taking the incidence of AML 4.3 per 100,000 from previous literature.[10]

Inclusion Criteria: All newly diagnosed cases of AML irrespective of age group or gender were included in the study.

Exclusion Criteria: Previously diagnosed patients on treatment, relapsed cases of AML, AML M3, therapy-related AML, and AML transformed from other haematological disorders were excluded.

Informed consent was taken from all patients. A detailed history with a complete physical examination was conducted on each patient. Complete blood counts(CBC) were performed on Sysmex automated haematology analyzer XN-3000 and the haematological parameters were recorded. Peripheral blood smears were stained with Leishman and Giemsa stains and inspected under a microscope. Bone marrow aspiration and trephine biopsy were done. Diagnosis of AML was made based on morphology and blasts percentage on the peripheral blood and bone marrow (aspirates/biopsies). All cases were classified according to FAB subtypes.[11] Bone marrow blasts morphology and percentage were noted. Conventional karyotyping was performed on all samples. Blood or bone marrow specimens were treated using the standard protocols for sample cultures. 10µL of the Meta systems XL p53 probe was used to perform FISH testing. Five hundred nuclei per assay were studied using a fluorescent microscope. The del 17p positivity or negativity was observed for each case. SPSS ver 23 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were calculated as frequencies and percentages.

RESULTS

In our targeted population of 80 patients, there were 25(29.8%) females and 59(70.2%) males. The mean age of presentation was 36.3±1.6 years. The mean total leucocyte count (TLC)was 31.2±4.2×10^9/L, the mean haemoglobin was 9.6±0.2 g/dL, and the mean platelet count was 69.3±4.5×10^9/L. In addition, 9.5% of all patients had involvement of lymph nodes in one or multiple groups, and the percentage of patients with hepatomegaly and splenomegaly were 15.5% and 31%, respectively. The most frequent FAB subtype was noted to be AMLM2 in patients with AML (42.9% of all the patients). Table-I classifies patients according to the FAB subtype of AML. Interphase FISH analysis was performed for all samples under study. 17p deletion was detected in 08 patients (9.5%) of 84 patients with AML (Table-II). In patients with 17*p* deletion, the mean TLC was 12.32±10.36x10^9/L, the mean platelet count was 80±26.73, and the mean haemoglobin was 12.27±4.65g/dl. Out of 8 cases with 17p deletion, one had AML M1, four had AML M2, one patient had AMLM4 and two had AML M5. Prominent clinical features among patients with del17p included fever and pallor.

Table-I : Acute Myeloid Leukemia French American British (FAB) Subtype (n=84)

FAB Subtype	n(%)
M0	7(8.3%)
M1	12(14.3%)
M2	36(42.9%)
M3	--
M4	21(25%)
M5	7(8.3%)
M6	1(1.2%)
M7	0(0)

Table-II : Frequency of 17p Deletion(n=84)

Del17p		
Present	**Absent**	**Total**
08(9.5%)	76(90.5%)	84(100%)

Patients were divided into two groups based on the presence or absence of 17p deletion (Table-III). The clinical-haematologic features associated with 17p deletion are summarized in Tables IV & V.

Table-III: French American British Subtype of Acute Myeloid Leukemia with del17p

FAB Subtype of AML	Del17p	
	Present	Absent
Mo	0(0%)	7(8.3%)
M1	1(1.1%)	11(13%)
M2	4(4.7%)	32(38%)
M3	--	--
M4	1 (1.1%)	20(23.8%)
M5	2(2.3%)	5(5.9%)
M6	0(0%)	1(1.1%)
M7	0	0

Table-IV: Hematological findings in 17p Deletion (n=84)

Del 17p	MedianTLC (x10⁹/L)	Median Platelet Count (x10⁹/L)	Median Hb (g/L)	Blasts in peripheral blood (%)	Blasts in Bone Marrow(%)
Detected	16.2±10.36	80±26.73	9.2±4.65	46	60±18.5
Not detected	35.2±5.01	55±15.33	10.07±1.92	65	75±15.4

Table-V: Clinical features of Patients in 17p Deletion (n=84)

		17*p* Deletion	
		Detected (n=8)	Not detected (n=76)
Pallor	Present	6(75%)	60(78.9%)
	Absent	2(25%)	16(21%)
Jaundice	Present	0(0.0%)	4(5.2%)
	Absent	8(100.0%)	72(94.7%)
Liver	Present	1(12.5%)	12(2.63%)
	Absent	7(87.5%)	64(84.2%)
Spleen	Present	1(12.5%)	25(32.8%)
	Absent	7(87.5%)	51(67.1%)
Fever	Present	7(87.5%)	67(88.1%)
	Absent	1(12.5%)	09(11.8%)

DISCUSSION

The significance of cytogenetics in haematological and non-haematological malignancies has been proven worldwide. For the last two decades, diagnostic cytogenetics has been acknowledged as one of the most significant prognostic indicators in AML.[11,12] Cytogenetic studies have enabled us to determine risk-adjusted treatment approaches; and also serve as a most valuable predictive factor for treatment response Patients can be categorized into three major risk groups based on cytogenetic abnormalities they harbour. Data regarding cytogenetic profiles of patients with AML is relatively scarce in Pakistan. Thus more research is required to determine better risk-based targeted treatment approaches.[13]

The study has revealed many facts regarding AML. The mean age was 36±15 years, comparative to other studies in Pakistan,[10,11] Kulsoom *et al.*[12] reported mean age comparable to ours. Jahic *et al.*[5] reported a much higher age of 53 years in the Bosnian population. In our study, AML M2 was the most common FAB subtype in patients with AML (42.9% of all the patients), comparable to other studies in Pakistan.[11,1] Main clinical features of our group of patients were pallor and fever, which are also comparable to other published data.[14] Our study revealed the frequency of del 17p to be 9.5% which was comparable to published literature; Fenaux *et al.* reported frequency of 17pdel in AML to be 7.1%,[15] and Preudhomme *et al.* reported it to be 5-10%.[16] Watell *et al.* reported a higher frequency of 17pdel in AML(15%).[17] Koeffler *et al.* also reported a similar frequency of 15%.[18] Seifert *et al.* reported a much lower frequency of 5%.[2] In a study conducted at University Milano, Italy, del 17p was found in 5 out of 70 cases of AML.[19] In our study, of the 8 cases with 17p deletion, one had AML M1, 4 had AML M2, 1 had AML M4, and 2 had AML M5 indicating no preponderance of del17p in one particular FAB sub-type of AML. These findings were consistent with the study done in France by Pierre *et al.*[20] Median age of AML patients with 17p deletion in our study was 33 years; however, data from other published literature suggests a much higher median age of AML patients with del17p, i.e.>60years.[20,21]

Though our study suggests a relatively low frequency of del17p in AML(9.5%), it carries important prognostic value. T*P53* mutations associated with 17p deletion carry unfavourable prognostic implications in patients with AML; the patients are more resistant to standard chemotherapy and have overall short-term survival.[8] This is the only study conducted in Pakistan in which 17p deletion was studied in patients with Acute Myeloid leukemia. No such study has been conducted before in Pakistan.

RECOMMENDATIONS

The limited knowledge about molecular changes involved in AML may cause speculative elaborations based on limited evidence, correlations or theoretical modelling. Major scientific research advancement with extensive multi-centre studies having a higher study population with equal gender representation and more comprehensive disease management is expected in the next future.

LIMITATIONS OF STUDY

The study was conducted at a hospital in a developing country where the patients were predominantly from a rural catchment area. These patients are brought to the hospital, mostly, in deteriorating condition, rather than early reporting. Our study was limited by the small sample size, predominantly male population and lack of availability of previous documents.

CONCLUSION

Initial assessment and longitudinal monitoring of haematological parameters and physical signs and symptoms are advisable in patients with del 17p. Studies should be planned to assess whether any induction or consolidation regimen change may be helpful in clinical settings to prevent evolution into severe disease and death.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SJ & HMR: Data analysis, drafting the manuscript, critical review, approval of the final version to be published.

HSM & AMA: Data acquisition, critical review, approval of the final version to be published.

SF & HN: Data acquisition, conception, study design, data interpretation, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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