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Molecular Characterization of Flt3 Mutation in Acute Leukemia

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Authors' contributions

This work was carried out in collaboration among all authors. Author AR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KA, AAJ, KAM, RIM, IAB and AA managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Fms-like Tyrosine Kinase 3 (FLT3) has an important role to perform in hematopoietic malignancy pathogenesis. Hence the focus of several studies has recently been FLT3.
Objective: To determine the molecular characterization of FLT3 mutation in patients of acute leukemia.
Methodology: This descriptive analysis was carried out from January 2018 to December 2018 upon a sample of 94 newly diagnosed cases of acute leukemia (chosen via non-probability, consecutive sampling) presenting to the Department of Pathology, Liaquat University of Medical & Health Sciences, Jamshoro. After taking informed written consent, Data were obtained from laboratory records and patient interviews were noted down with the help of structured questionnaire. SPSS v. 20.0 was used for analysis of the obtained data.

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Results: The mean age of participants was 41 years (±19 SD). 59.57% of the sample comprised of males while the remaining 40.43% were females. Among the total of 94 patients studied, patients with acute lymphoblastic leukemia (ALL) were 41 in number while those with acute myeloid leukemia (AML) were 53. The polymerase chain reaction verified FLT3 mutations in 6 (11.32%) out of 53 AML cases and 2 (4.88%) among 41 ALL cases. In acute myeloid leukemia (AML) FLT3 mutation was more prevalent among the older age set (51 and above), while in acute lymphoblastic leukemia (ALL) the FLT3 mutation was more commonly seen a comparatively younger patient age set (21 to 30 years).
Conclusion: It was found out that the FLT3 mutations are not uncommon in our study setting. With a greater prevalence observed among older male patients. AML was more common than ALL, with greater incidence rate of FLT3 mutations observed in the AML patients.

Keywords: Fms-like tyrosine kinase 3; acute myeloid leukemia; acute lymphoblastic leukemia; molecular characterization; polymerase chain reaction.

1. INTRODUCTION

All types of cancer causes nearly twelve percent of all demise around the globe [1]. In the developed world, the 2nd leading cause of demise is cancer, besides diseases of cardiovascular origin, constituting of twenty one percent (2500000 deaths). In the developing world, cancer is ranked third as a mortality cause accounting for nearly ten percent (3800000) of all demise [2].

Aberrations in the DNA of certain cells are believed to cause cancer. Certain carcinogens (such as chemicals, tobacco smoking, radiation, pollution of environment, and viruses) may also introduce damages in the DNA sequence. Erroneous replication of DNA may also be the defects in the DNA. Another probable factor leading to aberrations in the DNA is faulty gene inheritance[3].

Leukemia refers to malignancies of white blood cells. The malignancies are rare and arise from hematopoietic precursors.[4]This disease is divided and sub-divided into many types. Acute leukemia, as the name suggests, Comprises of malignant aberrations that are quickly fatal if not treated [5]. Their characteristic feature is sudden uncontrolled growth of immature hemopoietic cells at the cost of normal marrow function. The two most common forms, relevant to this study are Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) [6].

Owing to their vast and multi-factorial origin, the exact pathogenesis of both of these hematopoietic malignancies is not clear, but strong evidence exists that the fms-like tyrosine kinase 3 (FLT3) has an important role to play [7,8]. Research suggests that the FLT3 commands an important role hematopoietic cancer pathogenesis [9,10]. Studies reported expression of FLT3 protein in almost 100% of patients with acute myeloid leukemia (AML) and the same is found up to 50% in acute lymphoblastic leukemia (ALL) cases [11].

The magnitude of this problem in our region has not been adequately investigated and no published data available on molecular characterization of FLT3 mutation in acute leukemia. This study shall determine the molecular characterization of FLT3 mutation, thus helping understand the true burden of this disease and the underlying molecular pathology.

2. METHODOLOGY

This descriptive analysis was carried out from January 2018 to December 2018 upon a sample of 94 newly diagnosed cases of acute leukemia (chosen via non-probability, consecutive sampling) presenting to the Department of Pathology, Liaquat University of Medical & Health Sciences, Jamshoro. After taking informed written consent, Data were obtained from laboratory records and patient interviews were noted down with the help of structured questionnaire. SPSS v. 20.0 was used for analysis of the obtained data.

3. RESULTS

The mean age of the sample stood at 41 years (±19 SD). 59.57% of the sample comprised of males while the remaining 40.43% were females. Among the total of 94 patients studied, patients with acute lymphoblastic leukemia (ALL) were 41 in number while those with acute myeloid leukemia (AML) were 53. The polymerase chain reaction verified FLT3 mutations in 6 (11.32%) out of 53 AML cases and 2 (4.88%) among 41 ALL cases.

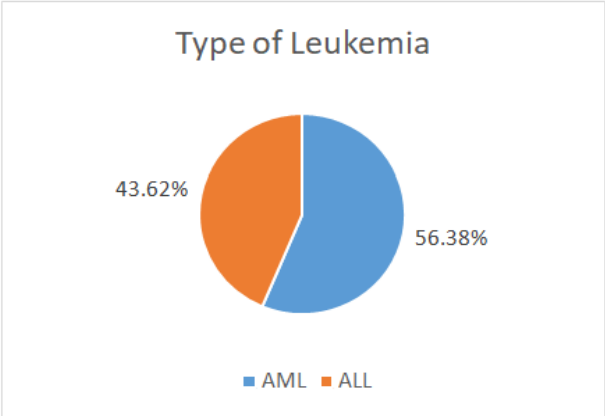

Fig. 1. Types of leukemia

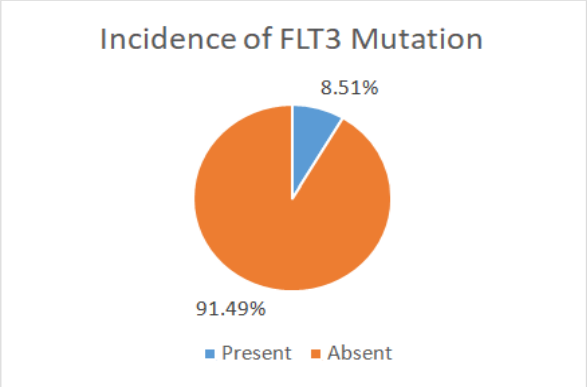

Fig. 2. Incidence of FLT3 Mutation

Table 1. Mutation in the leukemia types

Types of Leukemia	Mutation Present	Mutation Absent
Acute Myeloid Leukemia	6 (11.32%)	47 (88.68%)
Acute Lymphoblastic Leukemia	2 (4.88%)	39 (95.12%)

In acute myeloid leukemia (AML) FLT3 mutation was more prevalent among the older age set (51 and above), while in acute lymphoblastic leukemia (ALL) the FLT3 mutation was more commonly seen a comparatively younger patient age set (21 to 30 years).

4. DISCUSSION

No studies in the past have attempted to evaluate one individual cohort of formerly non-treated subjects with AML for FLT3 mutation and additional genetic abnormalities. The researchers of one study evaluated twenty eight relapsing patients of AML (mean age, fifty three years) enrolled on an array of separate protocols of treatment. They discovered that twenty three mutation in twenty eight of the relapsing patients of AML, with five subjects battling greater than one single mutation. A sum of sixty percent (seventeen of twenty eight) of subjects under study harbored a minimum of 1 mutation in FLT3, TP53 or RAS [12].

Despite the fact that the diagnostic and relapsing samples both contained mutations, eight mutations were exclusive to the relapsing cases while five were exclusive to the diagnostic lot. The clinical importance of FLT3 and other mutations in relapsing patients was also studies in the said research and it was unearthed that FLT3 and one other mutation were the only ones linked to a decreased survival rate while NRAS did not exhibit nay mal-effect on clinical outcome or disease prognosis [13,14].

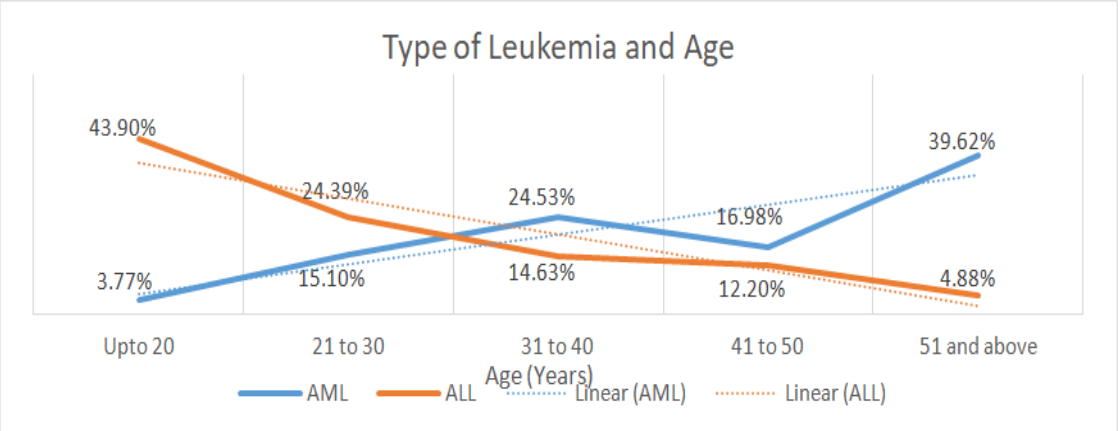

Fig. 3. Types of Leukemia and Age

Table 2. Presence of mutation according to age

Mutation	Up to 20 (Years)	21 to 30 (Years)	31 to 40 (Years)	41 to 50 (Years)	51 and above (Years)
Present	0	0	1	3	4

The mean age of the sample stood at 41 years (±19 SD) and the frequency of sample peaked at both extremes with most of the subjects being either ≤ 20 years or ≥ 50 years of age. This finding is synonymous with findings of other researchers that report that he peak incidence of ALL occurs between the ages of two to five years and consequently it is considered the most commonly occurring cancer among children (twenty five percent of all incidences of ALL). Additionally, ALL peaks again in the elderly but the incidence is much smaller than that among the young [15].

FLT3 mutation was more commonly seen a comparatively younger patient age set (21 to 30 years). A greater proportion of the total sample comprised of males, hence quantitatively, both AML and ALL groups had more males than females. However, when analyzed in detail, more of the males were in the AML group and more of the females were in the ALL group comparatively. Further strengthening our finding, evidence also exists that shows AML to be the most frequent acute leukemia in adults [16-18]. Thus our results stand as a testimony to the aforementioned facts.

Our study further showed that 59.57% of the sample comprised of males while the remaining 40.43% were females. While most literature fails to offer any conclusive evidence regarding whether each of the two discussed acute leukemia (ALL or AML), is more often seen in males or females, some literature does suggest that males are usually more at the receiving end of this condition with a greater propensity to develop ALL. There are however just as many researchers that have found women to be more often suffering and usually with AML, However, our research does not partake in the controversy and a non-significant male to female ratio is reported with although males seemingly reporting more with the conditions, but the greater numbers do not translate into any statistical significance [19, 20].

5. CONCLUSION

It was found out that the FLT3 mutations are not uncommon in our study setting. With a greater prevalence observed among older male patients. AML was more common than ALL, with greater incidence rate of FLT3 mutations observed in the AML patients.

CONSENT

After taking informed written consent, Data were obtained from laboratory records and patient interviews were noted down with the help of structured questionnaire. SPSS v. 20.0 was used for analysis of the obtained data.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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