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Profiling of Genetic Mutations among Adult Filipino Patients Diagnosed with Acute Myeloid Leukemia using Fluorescence In Situ Hybridization from 2014 to 2021: A Single-Institution Study*

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ABSTRACT

Introduction. Among patients with Acute Myeloid Leukemia (AML), the karyotype at diagnosis is an important prognostic indicator for predicting outcomes. Several studies have been done to identify the most common cytogenetic abnormalities seen in patients in other countries, however, limited studies have been done in our setting.

Objective. The study aims to determine the most common abnormalities present among patients with AML referred for Fluorescence in situ Hybridization (FISH) at the National Kidney and Transplant Institute.

Methodology. The study included 131 adult patients with a mean age of 46. Fluorescence in situ Hybridization was used to identify the following cytogenetic abnormalities: t(8;21), 11q23 (MLL), 16q22 (CBFB-MYH11), t(15;17) (PML/RARA), t(9;22) (BCR/ABL), 7q31 deletion, and Monosomy 7.

Results. FISH was negative in 40% (n=53) of patients. 7q31 deletion is the most frequently identified cytogenetic abnormality among patients with a single abnormality (n=17, 13%) present and is the most frequently identified abnormality among patients with multiple abnormalities (n=26). 7q31 deletion is more frequently observed among patients between the ages 51 to 60 years old and among patients with AML with monocytic differentiation. 22% (n=29) of patients have multiple abnormalities, with the most common abnormalities to occur together are 7q31 deletion and t(8;21) (n=20, 15%). Patients with negative results and patients with multiple cytogenetic abnormalities are commonly seen within the 41 to 50 age group.

Conclusion. The current study provides a single-institution view of the cytogenetic abnormalities among adult Filipino patients with AML using FISH. Further investigation on the clinical history of these patients, with correlation with other methods, as well as epidemiologic studies are needed to better understand the similarities and differences seen from previously reported incidences.

Key words: acute myeloid leukemia, fluorescence in situ hybridization, cytogenetics, profiling, hematology, Filipino

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INTRODUCTION

Acute Myeloid Leukemia (AML) is a hematologic malignancy that is characterized by increased blasts of myeloid lineage in the bone marrow to the point of detection in the peripheral blood and overwhelms the synthetic capacity of the bone marrow.[1] It is the most common acute leukemia among adults, and the incidence increases with age. The age-adjusted incidence of AML for all races in 2018 is 4.3 per 100,000 persons with a higher male-to-female ratio (5.2 : 3.6).[2]

It is a heterogeneous disease not only regarding morphology and clinical presentation but in the sense that they entail genetic alterations and epigenetic changes in the hematopoietic cells that regulate its growth and differentiation that can be detected through molecular and cytogenetic methods.[3] Various structural and numeric cytogenetic aberrations have been identified which has diagnostic and prognostic implications.[4–6] These rearrangements result in fusion genes that encode for an abnormal chimeric protein required for

leukemic transformation. Some of these alterations have characteristic immunophenotypes, like t(15;17) which results in Acute Promyelocytic Leukemia (APL). Moreover, these alterations have changed our view on how we classify AML as several of these cytogenetic abnormalities have become essential diagnostic criteria for certain subtypes of AML, bypassing the required 20% blast cut-off previously set by the World Health Organization (WHO) Classification of Hematolymphoid Tumors.[7]

These cytogenetic findings thus become an important prognostic indicator used in the clinical management of patients with AML.[8] Pretreatment karyotype is an important prognostic risk factor for achieving complete remission, disease-free survival, and overall survival in adult and pediatric patients with AML, hence, detection of these genetic abnormalities is now included in the routine diagnostic workup of newly diagnosed patients with AML.[9,10] Cytogenetics are also used to stratify patients into distinct prognostic groups to provide risk-adapted chemotherapy protocols.[11] Cytogenetic profiling of AML has been undertaken among patients in other countries,[1,3,12–15] but none so far has been done among Filipinos.

This investigation aims to determine the local prevalence of cytogenetic abnormalities as detected by FISH among patients referred to the National Kidney and Transplant Institute Medical Laboratory (NKTIML) from January 2014 to December 2021.

METHODOLOGY

Study design

This research is a retrospective cross-sectional study which utilized data from the FISH studies performed at the Fluorescence In situ Hybridization and Cytogenetics Section of NKTIML.

Study population

The study included all FISH studies done at the NKTIML from the years 2014 to 2021, adhering to the following criteria: 1) Adult patients (Ages 18 and older) referred to the NKTIML for AML panel by FISH; 2) Diagnosed with AML according to the WHO Classification which includes bone marrow biopsy and/or flow cytometry studies.

Specimens failing to adhere to the criteria, as well as those affected by the following circumstances were excluded: 1) Patients with FISH studies for other malignancies; 2) Patients with clinical diagnosis with AML which cannot be proven through bone marrow biopsy and flow cytometry; 3) Patients with FISH studies for AML where no clinical information or diagnosis is available.

Method sampling

Total enumeration sampling was done. The NKTIML logbooks and laboratory database, accessible through laboratory information system, were reviewed for FISH studies and any bone marrow biopsy and/or flow cytometry studies.

Data collection

All data were collected over three (3) months by the principal investigator under close monitoring by a consultant pathologist. Data collection took place in the FISH and Cytogenetics Section and access to materials was limited to the investigators and medical technologists assigned to the FISH section. The results of the FISH studies of samples that fit the inclusion criteria were sub-classified where appropriate: Negative FISH, t(8;21), MLL (11q23), CBFB-MYH11 (16q22), t(15;17), t(9;22), 7q31 deletion, Monosomy 7 and multiple cytogenetic abnormalities (defined as having more than one cytogenetic abnormality). Patients were divided into seven age groups.

Ethical considerations

Patient confidentiality was ensured during data collection and encoded using numerical patient identifiers. This research protocol adheres to international ethical standards as provided by the International Conference on Harmonization Good Clinical Practice guidelines (ICH GCP) and National Ethical Guidelines for Health and Health-Related Research. Permission to access relevant laboratory records and medical information databases was secured upon approval of the chairperson of the Department of Pathology and Laboratory Medicine and head of the FISH section.

Statistical analysis

The percentage of cytogenetic abnormalities in the different age groups was computed. Chi-square test was used to analyze the difference in cytogenetics among the different age groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Patient characteristics

Between January 2014 to 2021, 131 patients were included in the study. The average age of the patients included in this research is 46 (SD 16.15). There were 74 males and 57 females. There were 69 bone marrow samples and 62 peripheral blood samples. The average percent increased blast is 53% (SD 22.8). AML was the most common diagnosis among patients included in the study, followed by AML with monocytic differentiation (Table 1).

Cytogenetic abnormalities

Cytogenetic abnormalities seen among patients with AML are shown in Table 2. Among AML patients, no mutations were detected in 53 patients (40%). Cytogenetic abnormalities were detected in 60% (n=78) of patients. There were 29 patients (22%) with multiple abnormalities. The most common single mutation was 7q31 deletion (n=17, 13%), followed by t(8;21) (n=16, 12%), and t(15;17) (n=10, 8%). One patient (1%) with MLL (11q23), 4 patients (3%) with t(9;22), and 1 patient (1%) with Monosomy 7. There were no patients seen who harbor the CBFB-MYH11 (16q22) mutations. Among patients with multiple abnormalities, 7q31 deletion was still the most common mutation seen (n=26, 20%). Whereas the most common mutations seen together were t(8;21) + 7q31 deletion (n=20, 15%).

Table 3 shows the age-specific proportions of the cytogenetic abnormalities. The peak incidence of AML was 41 to 50 years old, with a mean age of 46. Most of the patients with negative FISH were between 41 to 50 years old. The

Table 1. Demographic profile of the patients

Patient's profile	Count (%), Mean ± SD
Age, mean ± SD	46 ± 16.15
Sex	
Male	74 (56.49%)
Female	57 (43.51%)
Blasts (%), mean ± SD	53 ± 22.8
Specimen	
Bone marrow	69 (52.67%)
Peripheral blood	62 (47.33%)
Diagnosis	
AML†	58 (44.27%)
AML† with monocytic differentiation	46 (35.11%)
APL‡	10 (7.63%)
AML† Minimally differentiated	4 (3.05%)
AML† with Myelomonocytic differentiation	1 (0.76%)
AML† with Erythroid Differentiation	1 (0.76%)
AML† vs. APL‡	1 (0.76%)
AML† with monocytic differentiation vs. APL‡	4 (3.05%)
AML† with Aberrant B-lymphoid expression	1 (0.76%)
Mixed Phenotype Acute Leukemia (Myeloid + B-Lymphoid)	1 (0.76%)
AML† with myelofibrosis	1 (0.76%)
AML† with history of Chronic Myelogenous Leukemia	1 (0.76%)
AML† with history of RAEB§ Type I	1 (0.76%)
AML† with history of Breast cancer	1 (0.76%)

†AML, Acute Myeloid Leukemia
‡APL, Acute Promyelocytic Leukemia
§RAEB, Refractory Anemia with Excess Blasts

Table 2. Cytogenetic findings in AML patients

Cytogenetic subtype	All AML patients (N=131)	
	Count (n)	Percent (%)
Negative FISH	53	40
Single abnormalities	49	38
t(8;21)	16	12
t(9;22)	4	3
7q31 deletion	17	13
(16q22)	0	0
(11q23)	1	1
t(15;17)	10	8
Monosomy 7	1	1
Multiple abnormalities	29	22
t(8;21) + 7q31 del	20	15
11q23 + 7q31 del	2	1
11q23 + t(9;22)	2	1
t(8;21) + 11q23 + 16q22 + 7q31 del	1	1
11q23 + 16q22	1	1
t(8;21) + 7q31 del + Monosomy 7	1	1
t(15;17) + 7q31 del	1	1
t(9;22) + 7q31 del + Monosomy 7	1	1
Total	**131**	**100**

AML, Acute Myeloid Leukemia

t(8;21), 7q31, t(15;17), and multiple abnormalities were significant in the Chi-square test for the difference. There is a significant difference between the number of AML patients in each age group. Patients between 41 to 50 years old also exhibited a higher number of patients diagnosed with t(8;21) and the highest number of cases with multiple abnormalities. Patients between 51 to 60 have the highest number of 7q31 deletions. The age group 21 to 30 has the highest number of patients diagnosed with t(15;17).

Tables 4 and 5 summarize the cytogenetic abnormalities per morphologic subtype. There were only 3 subtypes that have p-values since the rest had very few cases to be analyzed separately. t(8;21) was seen in 11 cases of AML. t(15;17) was seen in 7 cases of APL (including microgranular variants) and 3 cases in whom APL was considered versus AML and AML with monocytic differentiation. 7q31 deletion is seen in 7 cases of AML with monocytic differentiation. Of note, two patients with known Chronic Myelogenous Leukemia in leukemic transformation, both retained t(9;22). Fourteen patients with multiple abnormalities were AML, and 12 patients with multiple abnormalities were diagnosed with AML with monocytic differentiation. The t(8;21) + 7q31 deletion were the most common cytogenetic abnormalities to occur together (n=20) and is seen most commonly among patients with AML (n=11) and AML with monocytic differentiation (n=7).

The study was conducted to determine the most common cytogenetic abnormalities seen among patients with AML using FISH studies performed at our institution. Karyotyping at the time of diagnosis is essential, not only to the pathologist to confirm the diagnosis, but also to the clinician, whose decision to start treatment, as well as, to stratify patients into prognostic groups, relies on this information.

In the current study, the peak incidence of AML occurs at 41-50 years with a mean age of 46 years old which is younger than in the study by Byun et al (51 years old)[12] but older as in the studies performed by Elnaggar (36.5 years old)[1] and Meng (39 years old).[3]

Unlike in the studies done by Elnaggar, Meng, Byun et al., and Shaikh, 7q31 deletion (13%), is as common as the t(8;21) (12%).[1,3,12,14] Across different studies, the current study shows a higher percentage of patients with

Table 3. Age-specific proportions of cytogenetic abnormalities

Cytogenetic subtype	count (n)	group (≤20)	Age group (21-30)	Age group (31-40)	Age group (41-50)	Age group (51-60)	Age group (61-70)	Age group (71-80)	Age group (>80)	*p*
Negative FISH	53	3	9	7	11	8	8	5	2	0.214185
t(8;21)	16	0	3	2	6	3	2	0	0	0.035994*
t(9;22)	4	0	1	1	1	0	1	0	0	0.779774
7q31 deletion	17	1	2	3	2	7	2	0	0	0.014415*
(16q22)	0	0	0	0	0	0	0	0	0	NA
(11q23)	1	0	0	0	0	1	0	0	0	NA
t(15;17)	10	0	4	3	1	1	1	0	0	0.025164*
Monosomy 7	1	0	1	0	0	0	0	0	0	NA
Multiple cytogenetic abnormalities	29	1	2	5	11	6	2	2	0	0.001841*
Total	131	5	22	21	32	26	16	7	2	

*$p<0.05$. is considered significant in 95% CI.

Table 4. Cytogenetic abnormalities per morphologic subtype

Cytogenetic Abnormalities per Subtype	t(8;21)	11q23	16q22	t(9;22)	t(15;17)	7q31 deletion	Monosomy 7	Total	*p*
AML†	11	0	0	2	0	8	1	**22**	0.00000*
APL‡	0	0	0	0	6	0	0	**6**	0.00000*
AML† with monocytic differentiation	5	0	0	0	0	7	0	**12**	0.00002*
APL‡ Microgranular variant	0	0	0	0	1	0	0	**1**	NA
AML† vs APL‡ Microgranular variant	0	1	0	0	0	0	0	**1**	NA
AML† with monocytic differentiation vs. APL‡ Microgranular variant	0	0	0	0	2	0	0	**2**	NA
APL‡ Microgranular variant vs. AML† with monocytic differentiation	0	0	0	0	1	0	0	**1**	NA
AML† Est case of CML§	0	0	0	1	0	0	0	**1**	NA
AML† with previous diagnosis of breast cancer	0	0	0	0	0	1	0	**1**	NA
AML† with minimal differentiation	0	0	0	0	0	1	0	**1**	NA
Mixed phenotype Acute Leukemia (B/Myeloid) Est CML§	0	0	0	1	0	0	0	**1**	NA
Total	**16**	**1**	**0**	**4**	**10**	**17**	**1**	**49**	

*p<0.05 is considered significant in 95% CI.
†AML, Acute Myeloid Leukemia
‡APL, Acute Promyelocytic Leukemia
§CML, Chronic Myelogenous Leukemia

Table 5. Cytogenetic abnormalities per morphologic subtype in patients with multiple abnormalities

Cytogenetic Abnormalities per Subtype	t(8;21) + 7q31	11q23 + 7q31	11q23 + t(9;22)	t(8;21) + 11q23 + 16q22 + 7q31	t(8;21) + t(9;22) + 7q31	t(8;21) + 7q31 + Monosomy 7	11q23 + 16q22	t(15;17) + 7q31	t(9;22) + 7q31 + Monosomy 7	Total	*p*
AML†	11	0	1	0	0	1	0	0	1	**14**	0.0001*
APL‡	0	0	0	0	0	0	0	1	0	**1**	NA
AML† with monocytic differentiation	7	2	0	1	1	0	1	0	0	**12**	0.0001*
AML† with minimal differentiation	1	0	0	0	0	0	0	0	0	**1**	NA
AML† with aberrant B lymphoid expression	1	0	0	0	0	0	0	0	0	**1**	NA
Total	**20**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**29**	-

*p<0.05 is considered significant in 95% CI.
†AML, Acute Myeloid Leukemia
‡APL, Acute Promyelocytic Leukemia

chromosome 7 abnormalities compared to other studies where the more common findings are translocations t(8;21),[3,12,14] t(15;17)[1] and Trisomy 8.[15,16] 7q31 deletion is also the most common mutation seen among patients with multiple abnormalities seen in 26 cases, similar to the study done by Byrd et al in 2002, wherein deletions involving 7q rarely occur as isolated aberrations.[16] The aberration is also seen significantly among patients with AML with monocytic differentiation. Now the literature regarding the immunophenotype and morphology among patients with 7q31 deletions or mutations in chromosome 7 is limited and requires further study. A study done by Chen, Wood, and Cherian, analyzed the flow cytometry parameters among Myelodysplastic Syndrome (MDS), Myeloproliferative neoplasms (MPN), and AML patients with monosomy 7 and 7q deletions. An increase in CD14 expression on maturing granulocytic cells was seen more frequently in myeloid neoplasms with monosomy 7 than in 7q deletions. CD14 is a GPI-anchored protein expressed among monocytes.[17] 7q31 deletions are associated with a poorer prognosis among patients with AML[16] and in the recent WHO Classification are linked with Myelodysplastic Syndrome and Acute Myeloid Leukemia as well as secondary forms of AML and MDS.[11,18] The mechanism on how mutations in chromosome 7 drive tumorigenesis is still poorly understood and it is hypothesized that a possible tumor suppressor gene that resides in the long arm of chromosome 7 is lost among patients with Monosomy 7 or in 7q deletions.[19] Several studies have tried to investigate such a phenomenon. McNerney et al., demonstrated that CUX1, a tumor suppressor gene in the long arm of chromosome 7 is inactivated among patients with AML.[20]

A negative FISH result was seen in 40% of the population. This is a similar finding to the study done by Byun et al. (42.3%),[12] however, is lower than in the study done by Meng (69.6%)[3] and Byrd (48%)[16]. This could mean that either there are no cytogenetic abnormalities present or that there are cytogenetic abnormalities present that are not included in the FISH panel currently done in our institution. In our institution, commercially available probes (Abbott Laboratories, Abbott Park, Illinois) were used. These are available for panel testing consisting of t(8;21), MLL (11q23) rearrangement, CBFB-MYH11 (16q22), t(15;17), t(9;22), 7q31 deletion, and Monosomy 7, while other available markers such as -5/5q deletion, ETV6 mutations, TP53 deletion, and 9q34 rearrangements can be ordered individually. A review article by Gonzales and Mikhail lists other recommended FISH markers, mainly associated with intermediate to poor risk among patients with AML, such as Trisomy 8, MLL gene (11q23) fusion partners, inv(3)(q21q26) or t(3;3)(q21;q26) with MECOM (EVI1) aberrant expression, and t(6;9)(p22.3;q34) with DEK-NUP214 fusion, but these are currently not available in our institution.[21] The NCCN also recommends karyotyping, multiplex gene panels, and next-generation sequencing analysis to develop a more comprehensive diagnostic and prognostic assessment.[11] Patients with multiple abnormalities comprise approximately one-fifth of the population, ranging from 2 up to 4 mutations. A complex karyotype, defined as having ≥3 abnormalities cannot be assumed since one method of detection was used. There are, however, three patients (2%) in the population that meet this requirement which is seen lower in frequency than in the study done by Byun et al. (12.5%)[12]

and Shaikh (9%).[14] An investigation on the clinical history of these patients, when correlated with other molecular and cytogenetic studies can give us more information to better understand the pathogenesis, epidemiology and clinical and laboratory features. Further, the differences in demographic characteristics, ethnicity, socio-economic, environmental, and genetic factors may also be explored.

CONCLUSION AND RECOMMENDATIONS

The current study provides a single-institution view of the cytogenetic abnormalities among adult patients with AML using FISH. The results of the study showed that the most frequent cytogenetic abnormalities are 7q31 deletion followed by t(8;21) as the most common mutations seen among patients with single mutations whereas 7q31 deletion is the most frequent abnormality seen overall among patients with multiple mutations. The study also found 7q31 to be frequent among patients with AML with monocytic differentiation. Further investigation on the clinical history of these patients, with correlation with other methods as well as epidemiologic studies can be done in the future to confirm the findings of the study and provide more information to better understand the possible underlying mechanisms.

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STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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