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Adverse Drug Events and Predictors of One Year Survival among Adult Patients with Acute Myeloid Leukemia in a Kenyan Tertiary Health Facility

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Abstract

Background: Treatment of acute myeloid leukemia is a challenge because of the adverse drug events associated with therapy and the heterogeneous nature of the subtypes. Research on improving overall survival of patients based on different regimens, reduction of adverse drug events, clinical characteristics and the type of acute myeloid leukemia is critical.

Objective: The study evaluated the adverse drug events and predictors of survival among adult patients with acute myeloid leukemia in a Kenyan tertiary health facility.

Methodology: A retrospective hospital-based longitudinal study was adopted on 155 eligible patients at Kenyatta National Hospital. Patient records for the period between January 2014 and September 2019 were selected using simple random sampling. Data was analyzed using STATA version 14. Both inferential and descriptive statistics were determined. The level of significance was set at p=0.05.

Results: The average age of the participants was 43.78 (± 17.83) years with a female gender predominance (56.77%). The most common adverse drug events were neutropenia (29, 18.71%), myelosuppression (27, 17.42%), nausea (24, 15.48%), hepatotoxicity (21, 13.55%) and constipation (11, 61%). Predictors of one year survival were the low blast count following chemotherapy (P=0.021), thrombocytopenia (P=0.006), kidney failure (P=0.005) and central nervous system dysfunction (P=0.043). A poor prognosis was associated with AML FAB M6 (p=0.025).

Conclusion: Acute myeloid leukemia in adults has poor prognosis but chemotherapy especially induction with cytarabine and daunorubicin improves overall survival rate. Adverse drug events are common.

Keywords: Acute Myeloid Leukemia; Survival; Adverse Drug Events; Predictors; Regimen

List of abbreviations: AML: Acute Myeloid Leukemia; CD: Cluster of Differentiation; HLA-DR: Human Leukocyte Antigen -DR Isotype; MPO: Myeloperoxidase

Introduction

Acute myeloid leukemia (AML) is characterized by the rapid growth of abnormal cells that build up in the bone marrow and blood and interfere with normal blood cell production [1]. Symptoms may include feeling tired, shortness of breath, easy bruising and bleeding, and increased risk of infection. Occasionally, spread may occur to the brain, skin, or gums. It progresses rapidly and is typically fatal within weeks or months if left untreated [1,2]. Risk factors include smoking, previous chemotherap y or radiation therapy, myelodysplastic syndrome, and exposure to the chemical benzene. The underlying mechanism involves replacement of normal bone marrow with leukemia cells, which results in a drop in red blood cells, platelets, and normal white blood cells. Diagnosis is generally based on bone marrow aspiration and specific blood tests [3]. AML has several subtypes for which treatments and outcomes may vary.

Global cancer registry statistics rank AML between the eighth to the thirteenth of the cancer burden [4,5]. It is the most common type of acute leukemia in adults [6]. More than half of acute leukemia cases in Kenya have AML with a higher prevalence in males where it is the sixth cause of deaths due to cancer [7]. The five-year disease-free survival rate ranges from 10 to 15 % with low dose maintenance therapy and 25-35% with intensive courses of therapy [8]. The most common cause of death is infections, followed by hemorrhage and organ failure [9,10].

Chemotherapy is still the main treatment for most types of AML [11]. The effectiveness of chemotherapy may be limited in some cases because the leukemic cells become resistant over time. Treatment depends on the type of AML and may include combination chemotherapy, targeted therapy with monoclonal antibodies or stem cell transplant using the patient's or donor cells. The chemotherapy drugs used most often are a combination of cytarabine and anthracyclines such as daunorubicin or idarubicin [12]. The side effects of these drugs depend on the type, dose and duration of administration. They include hair loss and gastrointestinal disturbances.

A lot of research has improved treatment outcomes in developed countries [13,14]. Major progress has been made in the management of complications like thrombocytopenia, unlike in developing countries. There is documentation of favorable prognosis with optimal treatment characterized by a stable, non-progressive period of the disease [15]. These countries report complete remission rates of 65-80% and 5-year overall survival rates of 30-50%. In developing countries the prognosis is poor [16]. One year survival is as low as zero and complete remission rates less than half of that reported in developed countries [17]. This study evaluated the adverse drug events and predictors of survival among adult patients with acute myeloid leukemia in a Kenyan tertiary health facility.

Materials and Methods

Study Design and site

This was a hospital-based longitudinal study involving 155 adult patients diagnosed with acute myeloid leukemia at Kenyatta National Hospital. The facility is the largest teaching and referral center in Kenya. It has a well-established cancer treatment unit.

Study population

All patients diagnosed with AML between July 2014 to September 2019 were considered.

Inclusion and exclusion criteria

Patients aged 18 years and above were included. The incomplete records were excluded.

Sample size and sampling technique

One hundred and fifty five patient records were selected. This number was determined using Fischer's formula with subsequent reduction for finite population. Simple random sampling method was used to select the patient records. This was accomplished using computer generated random numbers. Only those records that satisfied the inclusion criteria were selected.

Study variables

The outcome variables were one year survival following diagnosis and adverse drug events. The explanatory variables were sociodemographic characteristics, clinical profile at diagnosis and types of drug regimens used as well as the subtypes of acute myeloid leukemia.

Data collection techniques

The researcher perused all the records of patients diagnosed and managed for acute myeloid leukemia from year 2014 to 2019. Using computer generated random numbers the records were selected at random. A data collection form that had been pretested was used. The tool had several sections including patient's biodata, type of acute myeloid leukemia, clinical characteristics, drug regimens and length of survival after diagnosis**.** To ensure confidentiality and security, the data was password protected and backed up at appropriate intervals.

Data analysis

The collected data were entered into an excel sheet and cleaned before exporting to STATA version 14. Descriptive analysis was done for the sociodemographic factors, different types of AML, the prevalence of different clinical characteristics, drug regimens and treatment modalities, treatment outcome and safety data related to chemotherapy. Kaplan-Meier test was used to conduct survival analysis. Bivariate and multivariate logistic regression models were employed to identify the predictors of survival over one year period among patients with acute myeloid leukemia at 0.05 level of significance.

Results

The majority (88, 56.8%) of the patients were females and seventy-three (47.10%) of them were aged between 18 and 40 years while the mean was 43.8 (± 17.83) years (Table 1). Thirty-four (21.9%) of them had a normal body mass index. There was a positive family history of acute myeloid leukemia in 6 (3.9%) cases. Eight (5.1%) patients had a history of myelodysplastic disorders.

Variable	Frequency, n (%)
Sex	
Male	67(43.2)
Female	88 (56.8)
Age	
18-40	73(47.1)
41-60	48(31)
>60	34(21.9)
Body Mass Index	
<18.5	14(9.0)
18.5 to < 25	34(21.9)
25 to < 30	4 (2.6)

Variable	Frequency, n (%)
30≤	4(2.6)
History of cancer	
Glioblastoma multiforme	3 (1.9)
Breast cancer	2(1.3)
Stomach cancer	1(0.7)
Cervical cancer	1(0.7)
Family history of cancer	
Acute myeloid leukaemia	6(3.9)
Myelodysplastic disorders	8(5.1)
Chronic myeloid leukemia	3 (2.0)

Table 1: Sociodemographic characteristics

Prevalence of AML immunophenotypes

CD 117 was the most prevalent immunophenotypes at 23(14.8%), followed by CD 34 (22, 14.2%) and CD33 (19, 12.3%) as shown in Table 2.

Immunophenotypes	Frequency	Percentage
Cd117	23	14.8
CD34	22	14.2
CD33	19	12.3
MPO	17	11.0
CD13	15	9.7
HLA-Dr	15	9.7
CD45	7	4.5
CD7	6	3.9
CD 11c	4	2.6
CD 3	4	2.6
CD15	4	2.6
Tdt	2	1.3
Ki-67	2	1.3
Bcl 2	2	1.3
Cd 68	2	1.3
CD 64	3	1.9
CD 17	2	1.3
CD 2	2	1.3
CD 38	2	1.3
Others (CD5,CD14,CD19,CD7, CD 8,CD4,CD11b, Sudan black)	8	5.2
NOT SPECIFIED	56	36.1

Table 2: Prevalence of AML immunophenotypes

Types of drug regimens used to manage AML

At Induction, majority (30, 19.4 %) of patients were on a combination of cytarabine and doxorubicin followed by the combination of cytarabine with daunorubicin (4, 8.5%) and combination of cytarabine, doxorubicin, and etoposide (4, 8.5%) as shown in Table 3. It is important to note that some of the treatment regimen used in the induction phase were the wrong choice but majority of the patients received the recommended regimen.

Phase of treatment	Regimen	Frequency (n, %)
Induction	Cytarabine +Doxorubicin	30 (19.35%)
	Cytarabine +sDoxorubicin+Etoposide	4 (8.5%)
	Cytarabine+Daunorubicin	4 (8.5 %)
	Cytarabine+ Etoposide	1 (2.12 %)
	Cytarabine+Doxorubicin+Vincristine	1 (2.12 %)
	Cytarabine +Doxorubicin +Mercaptopurine	1(2.12 %)
	Cytarabine+Mercaptopurine+Doxorubicin+Etoposide	1 (2.12%)
	Intrathecal Methotrexate	1(2.12%)
	Cytarabine Only	1(2.12%)
	Doxorubicin+Daunorubicin	1(2.12 %)
Re-induction	Re-induction bone marrow transplant	
	Re-induction Cytarabine +Daunorubicin	1(2.12 %)
	Re-induction Cytarabine +Doxorubicin	4(8.5%)
	Re-induction ATRA	2(1.29 %)
	Re-induction Arsenic Trioxide +ATRA	1 (2.12%)
	Intrathecal methotrexate	1(2.12%)
Consolidation	Consolidation Cytarabine Only	3 (33.3 %)
	Consolidation Cytosine+Doxorubicin	3(33.3%)
	Consolidation Cytosine +Daunorubicin	1(11.1 %)
Maintenance	Mercaptopurine	2(66.7%)

Table 3: Types of drug regimens

A combination of cytarabine and doxorubicin was the most prescribed regimen for re-induction. For consolidation, cytarabine was majorly prescribed alone (3, 33.3 %) or in combination with doxorubicin (3, 33.3%). During the maintenance phase mercaptopurine was used.

Prevalence of adverse drug events

The prevalence of adverse drug events is shown in Table 4. The most common ones were neutropenia (29, 18.7%), myelosuppression (27, 17.4%), nausea (24, 15.5%), hepatotoxicity (21, 13.6%) and constipation (11, 6%). These were followed by hypotension (17, 11%), cardiotoxicity (16, 10.3%), and hypokalemia (15, 9.7%).

Adverse drug event	Frequency	Percentage
Neutropenia	29	18.7
Myelosuppression	27	17.4
Nausea	24	15.5
Hepatotoxicity	21	13.6
Constipation	18	11.6
Hypotension	17	11
Cardiotoxicity	16	10.3
Hypokalemia	15	9.7
Pulmonary edema	13	8.4
Infection	12	7.7
Brain damage	11	7.1
Nephrotoxicity	10	6.5
Tumor lysis syndrome	7	4.5
Coagulopathies	6	3.9
Eye toxicity	5	3.2
Fever	5	3.3
Hyperkalemia	4	2.6
Peripheral Neuropathy	3	1.9
Diarrhea	2	1.3
Hand-foot syndrome	1	0.7
Alopecia	1	0.7
Decreased appetite	1	0.7
Difficulty in movement	1	0.7

Table 4: Prevalence of adverse drug events

Clinical profile

The most common clinical manifestations among the patients was febrile illness (137, 88.4%) followed by anemia (111,71.6%), thrombocytopenia(100,64.5%), hemorrhage (99,63.9%),and nausea (66,42.6%) as shown in Table 5.

Sign or symptom	Frequency	Percentage
Febrile Illness	137	88.4 %
Anemia	111	71.6 %
Thrombocytopenia	100	64.5 %
Hemorrhage	99	63.9 %
Kidney damage	72	50.1%
Nausea	66	42.6%
Lymphadenopathy	42	27.10 %
Hyperuricemia	41	26.5 %
Liver Changes	72	23.5%
Splenomegaly	34	21.9 %
Gastritis	67	21.6%
Gum hypertrophy	32	20.7 %
Constipation	27	17.4%

Sign or symptom	Frequency	Percentage
Central Nervous system manifestations	48	15.5%
Oral Ulceration	42	13.6%
Visual changes	21	13.6 %
Hepatomegaly	33	10.7%
Joint Pains	27	8.7%
presence of Edema	22	7.10%
Diaphoresis	20	6.5%
Cardiomegaly	20	6.5%
Disseminate intravascular coagulation	4	2.6 %
Myeloid Sarcoma	4	2.6%
CNS leukemia	3	2%

Table 5: Prevalence of signs and symptoms

Kaplan-Meier estimate for overall Survival

Kaplan-Meier analysis showed that over 75% of the patients diagnosed with acute myeloid leukemia had a high probability of dying within the first three months of diagnosis (Figure 1). The longest survival period was about 30 months.

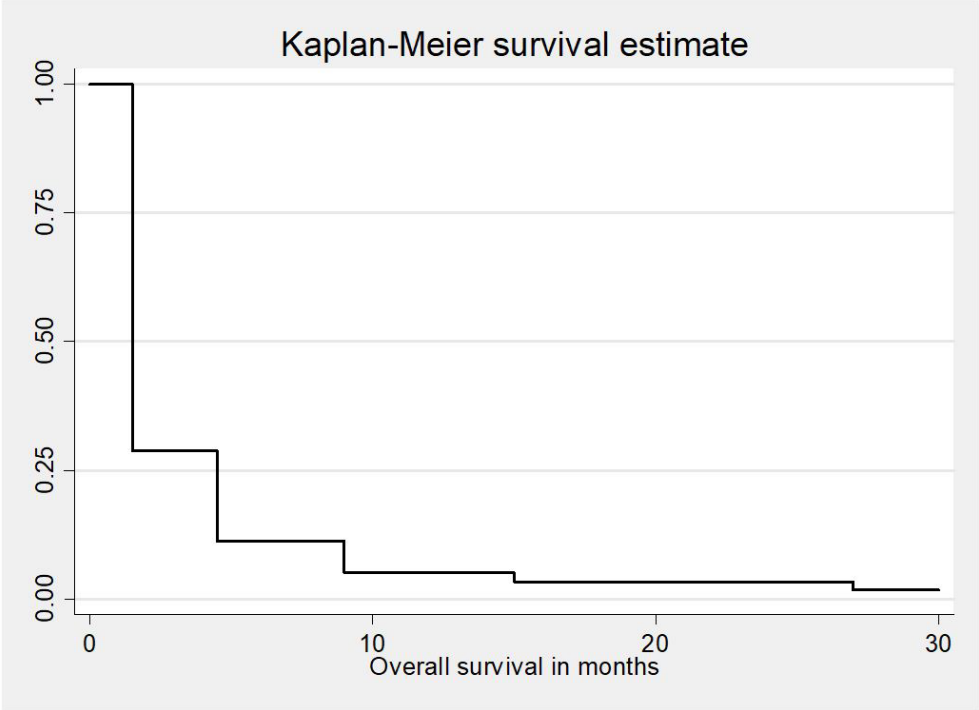

Figure 1: Kaplan-Meier survival estimate showing overall survival

Prevalence of AML FAB types and association with one year overall survival among adult patients with acute myeloid leukemia in Kenyatta National Hospital, Kenya

French-American-British classification for types of acute myeloid leukemia was done for 94 patients. The majority (37, 23.87%) of the patients had M2 followed by M1 (19, 12.26%) as shown in Figure 2. The French-American-British types with the least prevalence were MO, M5, and M8.There is an association that is statistically significant between one year survival and AML MO FAB type from Fischer's exact test (p (0.025).

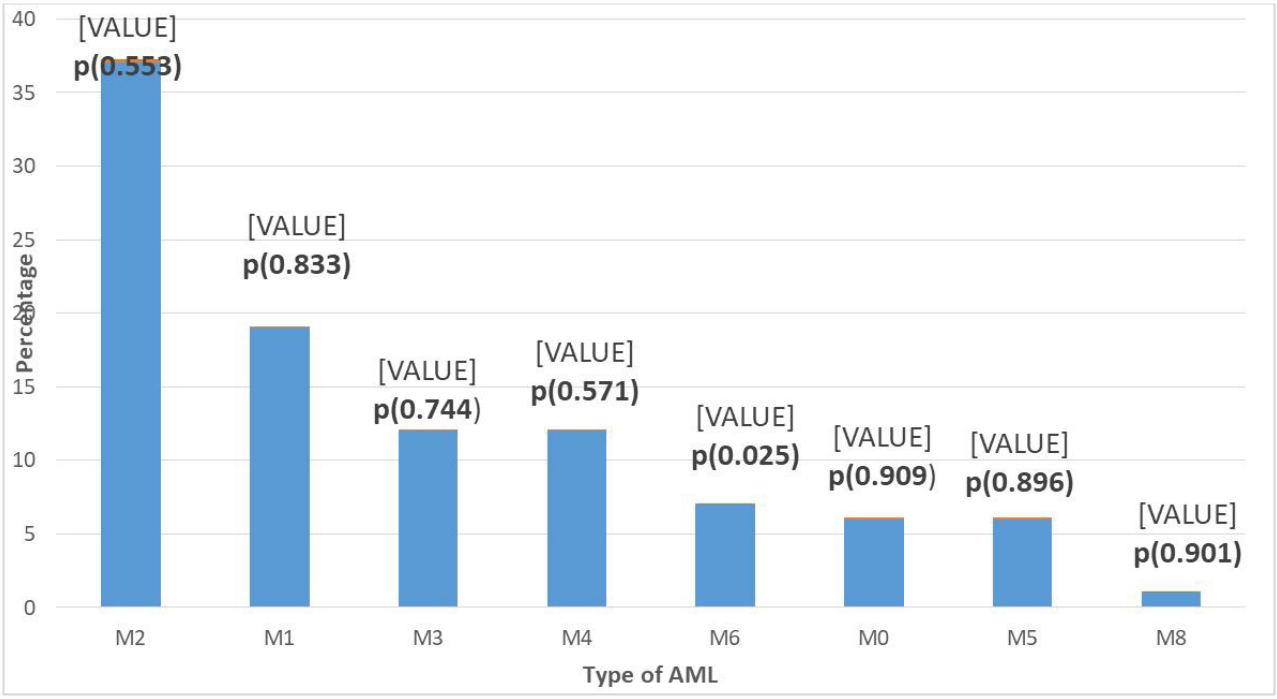

Figure 2: Graph showing distribution trend of types of acute myeloid leukemia according to French-American-British classification and association between AML FAB types and one year overall survival among adult patients in Kenyatta National Hospital, Kenya

Predictors of one year survival

Multivariate logistic regression showed five independent predictors of survival at the end of one year (Table 6). The dependent variable was whether the patient was alive or dead. The predictors were blast count after chemotherapy (p=0.021), thrombocytopenia (p=0.006), lymphadenopathy (p=0.006), kidney failure (p=0.005) and mental dysfunction (p=0.043) which included migraines, seizures and syncope.

Variables	Bivariate analysis		Multivariate analysis	
	COR (95% CI)	P-Value	AOR (95% CI)	P-Value
IMMUNOPHENOTYPES CD7	0.70(0.47,1.03)	0.075	0.23(0.032,1.43)	0.112
CD13	0.63(0.40,0.99)	**0.043***	0.11(0.004,2.62)	0.171
CD33	0.63(0.39,1.02)	0.059	18.26(0.66, 501.92)	0.086
CD45	0.68(0.45,1.02)	0.059	0.40(0.019,8.11)	0.548
HLA-Dr	0.65(0.41,1.03)	0.068	0.93(0.05,15.80)	0.958
CLINICAL CHARACTERISTICS AT DIAGNOSIS				
Blast count after chemotherapy	1.25(1.00,1.56)	**0.046***	1.44(1.06,1.97)	**0.021***
Thrombocytopenia	0.41(0.22,0.75)	**0.004***	0.30(0.13, 0.71)	**0.006***
Lymphadenopathy	0.61(0.36,1.04)	0.067	0.31(0.13,0.72)	**0.006***
Kidney failure	0.40(0.22,0.72)	**0.003***	0.34(0.16,0.72)	**0.005***
Cardiomegaly	3.98(1.36,11.58)	**0.011***	2.75(0.81,9.41)	0.106
Mental dysfunction symptoms	0.55(0.29,1.02)	0.059	0.44(0.19,0.97)	**0.043** *
Abscesses	0.62(0.38,1.02)	0.061	0.73(0.39,1.35)	0.308
TREATMENT				
Consolidation	9.97(1.2,81.76)	0.032	46.58(2.04,1063.83)	0.016

*- Statistically significant relationship

Table 6: Predictors of one year survival (deceased or alive) for acute myeloid leukemia

Discussion

There were more females than males patients in this study which contradicts the general observation where the disease has male preponderance [18]. This observation may be attributed to the several cancer treatment centers which are in close proximity and patients chose where to go. The majority of the patients were relatively young despite that the disease mainly afflicts old people [19]. This is largely because majority of the Kenyan population are relatively young. Majority of the patients had normal BMI although previous studies have demonstrated an association between high body mass index (BMI) and acute myeloid leukemia [20]. The global overall survival for patients with AML has consistently been low in the first one year for both developed and developing countries. The overall survival is determined by drug regimen, adverse drug events, the signs and symptoms and the type of acute myeloid leukemia among other factors. In developing countries, cytarabine and anthracycline regimens have been the mainstay treatment for all adult cases of acute myeloid leukemia. All-trans-retinoic acid and arsenic trioxide are used for acute pro-myelocytic leukemia [14]. It is important to note that some of the treatment regimen used in the induction phase were the wrong choice but majority of the patients received the recommended regimen.

Evidence highly recommends daunorubicin at doses of 45-90 mg/m^2 for three days to doxorubicin owing to the higher complete remission achieved with daunorubicin and less cardiotoxicity and myelosuppression [21]. The addition of a third drug including etoposide has shown no considerable benefit due to secondary malignancies despite increased remission rate and 50-60 mg/m^2 dose of daunorubicin has been shown to be less myelosuppressive than 12 mg/m^2 dose of idarubicin [22]. A combination of cytarabine and doxorubicin was the most prescribed regimen for induction. This is in contrast with the recommended National Comprehensive Cancer Network Guidelines 2017 that highly recommend daunorubicin to doxorubicin. Evidence has also shown that patients on daunorubicin have a lower relapse rate compared to doxorubicin [21].

The drugs used for consolidation and maintenance in our study are those recommended by National Comprehensive Cancer guidelines [21]. For the maintenance phase, mercaptopurine was administered since it confers an anti-relapse benefit in patients with acute pro-myelocytic leukemia who are ineligible for stem-cell transplantations [23]. Anthracycline-based regimens were administered for majority of the patients before determination of the cardiac function at the beginning of therapy which contrasts the recommended approach. This could possibly due to financial constraints. Non- anthracycline-containing regimens such as those with midostaurin and clofarabine as well as administration of IV fluids have been suggested for patients already presenting with an ejection fraction less than 45% [21]. Body mass index, neutropenia after chemotherapy and the consolidation phase of treatment were identified as independent predictors of survival rate. Studies have shown that increased body mass index increases the survival rate of patients with acute myeloid leukemia where obese patients were observed to tolerate the toxicity of the drugs better than other patients. High neutrophil count after chemotherapy improves overall survival [24]. The consolidation phase of chemotherapy increases the length of survival of patients with acute myeloid leukemia [25]. Delayed treatment reduced overall survival for patients who were already eligible for chemotherapy [26]. There is a strong association between decreased overall survival and more than five days of delay in chemotherapy initiation [27]. Patients with blasts positive for immunophenotype myeloperoxidase (MPO) showed an increase in the overall survival. Studies done to show a strong association between myeloperoxidase and increased overall survival have confirmed these findings [28]. Patients with a high incidence of death within one year had high blast count after chemotherapy. Other factors that reduced overall survival were presence of thrombocytopenia, lymphadenopathy, kidney failure and central nervous system manifestations which included migraines, seizures, and syncope at diagnosis. Studies have shown that all these clinical characteristics are positive predictors for death from acute myeloid leukemia within one year of diagnosis. CD13, CD7, CD33, CD45, and (Human Leukocyte Antigen-DR Isotype (HLA-DR) were associated with increased mortality. After multivariate analysis, it was noted that the immunophenotype that increased the chances of survival was CD33 [28].

From this study, the most prevalent French-American-British (FAB) types were M2, M1, M3 and M4 which is similar to a private hospital in Kenya and elsewhere in Africa [7]. From the Fischers exact test, FAB type M6 had a statistically significant association with one year survival among patients with acute myeloid leukemia where majority of the patients with FAB type M6 died within the first year. Evidence has shown that people with acute myeloid leukemia of the FAB M6 type have poor prognosis [29].

Conclusion

Acute myeloid leukemia has poor prognosis and adverse drug events are common among patients on chemotherapy.

Recommendations

Chemotherapy should be initiated early in patients with AML and adequate monitoring and treatment of adverse drug events adequately carried out.

Study limitations

Due to the retrospective nature of the study, missing data was a challenge. The number of patients eligible for chemotherapy based on kidney function and complete blood count results, was lower than the overall diagnosed number of patients with acute myeloid leukemia. Our study has several strengths despite these limitations.

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Conflict of interest

The authors declare no conflict of interest.

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The study was self-funded.

Availability of Materials and Data

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Permission to carry out the study was sought from Kenyatta National Hospital / University of Nairobi Ethics and research committee (approval number P199/03/2019). Consent and approval were sought from the Kenyatta National Hospital administration by registering the study with the Kenyatta National Hospital research and programs department. A letter of support from the Head of Department Hospital Management Information Information System in Kenyatta National Hospital was attached. The information from patient treatment files was treated with confidentiality and used for the intended purpose. Patient's inpatient or outpatient numbers were not recorded but were serialized with specific codes. This maintained the anonymity and privacy of the patients.

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