Clinical profile and treatment outcome of Acute leukemia patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

A three-year retrospective study

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Abbreviation

AAU……...Addis Ababa University
AL……...Acute Leukemia
ALL……Acute Lymphoblastic Leukemia
AML……...Acute Myeloid Leukemia
APL……Acute Promyelocytic Leukemia
ATRA…… All Trance-retinoic Acid
ATO……Arsenic Trioxide
BLCM…… Below Left Coastal Margin
BM……. Bone Marrow
CALGB…….. Cancer and Leukemia Group B
CLD……Chronic Liver Disease
cms…….…… Centimeters
CME……...Continuous Medical Education
CNS……Central Nervous System
CR……. Complete Remission
DAH……...Diffuse Alveolar Hemorrhage
EFS…… Event free survival
FAB……French-American-British
FMoH…… Federal Ministry of Health
GI……...Gastrointestinal
GVHD……Graft Versus Host Disease
Hgb……...……. Hemoglobin
HBV……...……Hepatitis B Virus
HCV……...Hepatitis C Virus
HIV……Human Immune-deficiency Virus
HSCT……... …… Hematopoietic Stem Cell Transplantation
ICH……Intracranial Hemorrhage
JVP…….Jugular Venous Pressure
LDH……...Lactate Dehydrogenase
M: F……...……Male to Female ratio
MRN……. Medical Record Number
PTE…….…...Pulmonary Thromboembolism
SNNPR…….. Southern Nations Nationalities and Peoples Region
TASH……Tikur Anbessa Specialized Hospital
TLS……...Tumor Lysis Syndrome
TB……...……..Tuberculosis
UK……...……. United Kingdom
US…… United States
WHO…… World Health Organization

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Abstract

Background

The incidence of acute leukemia is increasing worldwide. In Ethiopia, in terms of incidence among all cancer cases, it ranks fourth and fifth in men and women respectively. Despite acute leukemia being this prevalent nationally and even a more concerning issue in Tikur Anbessa Specialized Hospital(TASH) the largest hemato-oncology center in the country, there have been only few studies done on this area so far.

This study is important to have a contemporary data on the clinical presentation and outcome of acute leukemia patients and helps to put a light on gaps of acute leukemia care in for further detailed studies.

Objective

The Main objective of this study is to define clinical profile and treatment outcome of all patients above the age of 12 years and admitted with the diagnosis of acute leukemia at TASH from January 1, 2015 to December 31, 2017.

Methods

The study design is a retrospective cross sectional study which was conducted at TASH from June, 2018 to October, 2019. Structured questionnaire was use to collect data from medical record chart of patients diagnosed with Acute leukemia TASH from January 1, 2015 to December 31, 2017. Descriptive analysis and frequencies were done using the software IBM SPSS statistics data editor version 25 .0.

Result

There were a total of 235 patients above the age of 12 and diagnosed with acute leukemia and admitted to TASH from January 1, 2015 to December 31, 2017. Out of these patients, 59.1% had AML, 40% had ALL and 1 patient had a Bi-lineage leukemia and 1 other had unclassified leukemia. Males were dominant with M: F ratio of 1.58. Majority of patients were young in the age category between 12-30 years. The commonest FAB subtype of AML and ALL were M4 and L2 subtypes respectively. The commonest presenting symptom was symptoms of anemia (94%) and the commonest sign was pallor (89.4%). The commonest laboratory finding was anemia (96.2%) followed by thrombocytopenia (94.9%). Majority (64.6%) of patients had leukocytosis.
About 53.6% of patients were started on chemotherapy. Among these, 79.3% took intensive induction regimens while 12.7% patients took palliative treatment only. The commonest induction protocol used for ALL was CALGB, for Non M3 AML was 7+3 and ATRA+ Chemotherapy for patients with AML M3. Patients with AML had CR rates of 63.3% whereas ALL patients had CR rates of 92.9%. Default rates was 10.9% and induction death rate was 28.2% which w has high. The most common cause of death was neutropenic sepsis followed by intracranial hemorrhage. The rate of lost from follow up was very high with only 6 patients currently alive and on follow up.

Conclusion

The clinical presentation of patients with acute leukemia generally similar with most findings in the literature. However, acute leukemia occurred at a very young age compared with other studies. There is a very high early and induction mortality but comparable CR rates to most centers.

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1. Introduction

Acute leukemia is a type of malignancy characterized by a persistent proliferation of clonal and malignantly transformed blood forming cells arising from the bone marrow or the lymphoid organs which are often associated with fundamental genetic abnormalities. The clinical presentation of acute leukemia is associated with the replacement of marrow by malignant and rapidly dividing leukemic blast which interferes with the normal proliferation and differentiation of hematopoietic precursor cells. The clinical course is usually rapid and outcome is fatal, within three months, if untreated.[1]

Leukemia is one of commonly diagnosed cancers, estimated to have the 11th highest incidence of all cancers and acute leukemia per se represents a significant proportion of hematological malignancies worldwide. [2,3] Correspondingly, according to a paper published on cancer estimate, with regards to incidence, leukemia is the fourth commonest type of malignancy in men and the fifth commonest in females in Ethiopia which is quite a higher proportion in comparison to the global figures. [4,5]

In the United States of America, it was reported that hematologic malignancies accounted for approximately 6-8% of cancer incidence in both sexes, the incidence of acute leukemia being about 34 per million populations. [6] Studies from UK, Australia, Canada and Denmark have shown that the incidence of AML is rising in developed countries as the population becomes proportionally older. For example, Denmark has a high proportion of senior residents along with the highest reported incidence of AML at 5.4 cases per 100,000 person-years.[2,3,7] Similarly, ALL incidences are increasing globally and the case burden is expected to rise among adults in whom the disease is particularly fatal. Increasing age and male sex were the non-modifiable risk factors with the largest effects. [8]

Although consistent epidemiologic findings are expected with regards to particularly age and sex in most populations, a difference in the pattern of clinical presentation and distribution has been reported in various communities over the years. Given the marked disparity in the physical and social environment between the developed and developing countries, it is reasonable to suspect that there may be significant differences in the epidemiology and clinical profiles of hematological malignancies in developing part of the world when compared to that of the more advanced communities.[9]

Coming to the Ethiopian context, apart from the national estimates of cancer prevalence, there are only few researches done on acute leukemia. These few researches were done almost a quarter of a century back and it is difficult to believe that the findings of these old studies would reflect the current situation. One of the studies reported acute leukemia to be the commonest form of all types of leukemia in Ethiopia. In this study among the acute leukemia cases AML constituted 53.7 % whereas ALL contributed for the rest. [10]

Despite the growth of cancer incidence, the development of health care system meant to treat cancer cases in Ethiopia is lagging behind. Tikur Anbessa Specialized Hospital is the only setup in Ethiopia which is well experienced and fairly equipped with both diagnosis and treatment of acute leukemia and most of the other oncologic conditions. There are few other centers that are providing some services however these services are not comprhensive.[4]

According to the monthly audits of total admissions to the department of Internal Medicine in TASH acute leukemia cases are estimated to account up to 40% of each month's admissions to the Internal Medicine wards. However, due to the lack of recent studies as mentioned above the changing magnitude, clinical characteristics as well as treatment outcome of acute leukemia patients treated with the available setup is not documented either institutionally or nationally.

The outcome of treatment for leukemia and cancer in general are said to be unsatisfactory in developing countries like Ethiopia. Several factors might play a role for the poor outcome of such patients in developing countries, such as late presentation to hospital, limitation of diagnostic capacities and inaccessibility of appropriate therapies, blood and blood products. But all of these remain just speculations and individual opinions unless they are studied and documented. And it is quite hard for the health sector to target and tackle an uncertain assumption. Most of all, provision of any intervention depends on several factors, including disease burden, cost, and effectiveness. [10,11]

The value of studies on various health matters is indisputable. Having a national baseline data of any disease is crucial to recognize a change in the incidence, demographic characteristics and treatment outcome of a disease. Such type of baseline data can also be used to study treatment outcome predictors which is crucial in gauging measures, upgrading care and interventions at both national and institutional levels.

In addition, recognizing such diseases and understanding the magnitude will help to urge the government and policy makers to have a well set and decentralized national control and treatment plan towards acute leukemia and other oncologic conditions. It will also help in health planning, funding of treatment and further research projects on similar disease entities. Additionally, it helps in raising awareness to the general public as well as concerned bodies and international funding agencies.

2. Objectives

2.1. General Objective

- To study the clinical presentations and treatment outcome of patients diagnosed to have acute leukemia at TASH within three-year time, from January 1, 2015 to December 31, 2017

2.2. Specific Objectives

- To describe the clinical presentation of patients with acute leukemia admitted to TASH from January 1, 2015 to December 31, 2017
- To study treatment outcome of acute leukemia patients admitted to TASH from January 1, 2015 to December 31, 2017

3. Methods

3.1. Study Design

A retrospective cross sectional design was used to study the clinical profile and treatment outcomes among acute leukemia patients admitted to TASH from January, 2015 to December 2017.

3.2. Study Area

The study was done in Tikur Anbessa Specialized Hospital which is the largest governmental teaching hospital in Ethiopia located in the capital Addis Ababa. The hospital has served as a medical and health science teaching center for the country's biggest university, Addis Ahaba University.

It is estimated that it serves 370,000 - 400,000 patients a year and has more than 800 beds. It is also the first and the largest hospital to start hematology-oncology services in the country. The Internal Medicine department of TASH is one of the oldest departments and has around 100 beds. Among these around 38-40 of them are dedicated to hematology patients. There is also a separate hematology/oncology center located some 1.5 km away from the main compound which gives service to relatively stable patients on consolidation therapy.

The wards are organized in a way that they accommodate 6-7 beds in a room where most pre chemotherapy patient share rooms with other hematology patients like lymphoma. Whereas the others rooms which accommodate two patients in a room and two rooms with isolated beds are preserved for the most flail acute leukemia patients on induction chemotherapy.

With regards to care providers, there are four hematologists and one hematology fellow who are in charge of daily rounds and treatment decisions of admitted patients. There are also about 8-9 internal medicine residents, 8-10 interns, 16-18 nurses caring for these patients.

3.3. Study Period

The study was started on June 1, 2018 and was completed on October 30, 2019.

3.4. Study Population

3.4.1. Source population

All patients above the age of 12 and diagnosed to have acute leukemia and admitted to the Internal Medicine department of TASH within the study period from January 1, 2015 to December 31, 2017 will be included

3.4.2. Study Subject

All patients above the age of 12 and admitted to the Internal Medicine wards of TASH with the diagnosis of acute leukemia within the three-year period and whose medical record charts were available at the central medical record office of the hospital were included in the study.

3.4.3. Sample Size

Since acute leukemia is a relatively rare disease and the study is an institution based study, we included all available cases. Accordingly, all patients above the age of 12 and diagnosed to have acute leukemia and admitted to TASH from January 1, 2015 to December 31, 2017 were included in the study.

3.5. Data Collection

3.5.1. Inclusion Criteria

- All patients above the age of 12 who presented for care at the TASH and diagnosed to have acute leukemia and admitted to TASH from January 1, 2015 to December 30, 2017
- All patients had a confirmed pathologic diagnosis of acute leukemia

3.5.2. Exclusion criteria

- Patients suspected to have acute leukemia clinically but no pathologic diagnosis was made during their stay were excluded from the study.

3.5.3. Study variables

- Age
- Sex
- Time from symptom onset until presentation

- Time of treatment commencement
- Comorbid conditions
- WBC at presentation
- Type and subtype of leukemia
- Complete Remission
- In-hospital mortality
- Relapse

3.5.4. Operational Definition

- **Complete Remission**- defined as the eradication of all detectable leukemia cells (less than 5 percent blasts) from the bone marrow and blood and the restoration of normal hematopoiesis (>25 percent cellularity and normal peripheral blood counts)
- **Relapse**- the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission.
- **Refractory (resistant) disease**: defined as those patients who fail to obtain a CR with induction therapy, i.e., failure to eradicate all detectable leukemia cells (less than 5 percent blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (greater than 25 percent marrow cellularity and normal peripheral blood counts).
- **CNS Involvement**- ≥5 cells/mm3 of CSF analysis

3.6. Data collection and analysis methods

All patients who were diagnosed and admitted to the Internal Medicine Department (Hematology Unit) of TASH, Addis Ababa, from 1st of January, 2015 to 31th of December 2017 inclusive fulfilling the inclusion criteria were enrolled in the study. Data was collected from patients' chart with a structured questionnaire. Ward log books from each ward were used to obtain medical record numbers of patients diagnosed and treated for acute leukemia. All patients with preliminary diagnosis of acute leukemia, bicytopenia, and pancytopenia during admission were selected and screened for inclusion to the study. Roughly about one-third of the charts of such patients was lost from the central medical records office upon screening. Accordingly, among the records found, close to 600 medical charts were screened. And those patients who were

confirmed to have acute leukemia based on clinical features, blood counts, peripheral blood films and most importantly bone marrow examination either by pathologist or hematologist were included. These were around 235 cases which fulfilled the above criteria. Subsequently, specific information from the medical chart was filled on structured questionnaire prepared for this purpose.

The cases were characterized with respect to age, sex, morphological or histological type and subtype of leukemia, treatment status and outcome of treatment.

After data was collected it was edited and coded for analysis. Data entry and analysis was done using the SPSS statistical software version 25. Frequency tables and graphs were used to express the results.

4. Ethical Consideration

Ethical clearance was obtained from the ethical review committee at College of Heath Science, Addis Ababa University through the entrustment of the research coordinator's committee of department of Internal medicine.

5. Dissemination of research results

The result will be presented to the department of Internal medicine and if situation allows to the whole academic society of interest such as College of Health Science and AAU staffs. It will also be presented on various medical conferences and CME seminars if situations allow.

Research findings will be sent to both national and international medical journals for possible publishing and it will be disseminated through internet to different medical sites. Results will also be disseminated to other teaching and non-teaching hospitals, federal and regional health bureau in collaboration with the Federal Ministry of Health (FMoH).

6. Result

There were a total of 235 patients above the age of 12 diagnosed with acute leukemia and admitted to TASH from January 1, 2015 to December 31, 2017. Out of these, 139(59.1%) were diagnosed with AML, 94(40%) were ALL patients and 1 (0.45%) patient had a Bi-lineage leukemia and 1 other (0.45%) had unclassified acute leukemia.

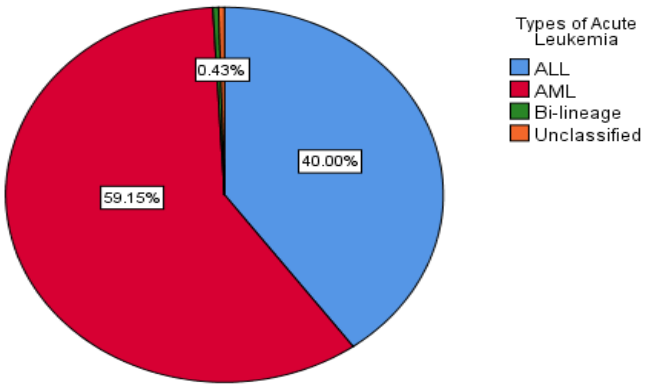

Figure 1: Types of Acute Leukemia

The age of patients ranged between 13 -76 years, median age at diagnosis was 27 years whereas the mean age at diagnosis was 32 years (SD±15.28). The median age for ALL was 23 years while for AML it was 32 years. Majority of the patients belonged to age categories of 13-20 followed by 21-30.

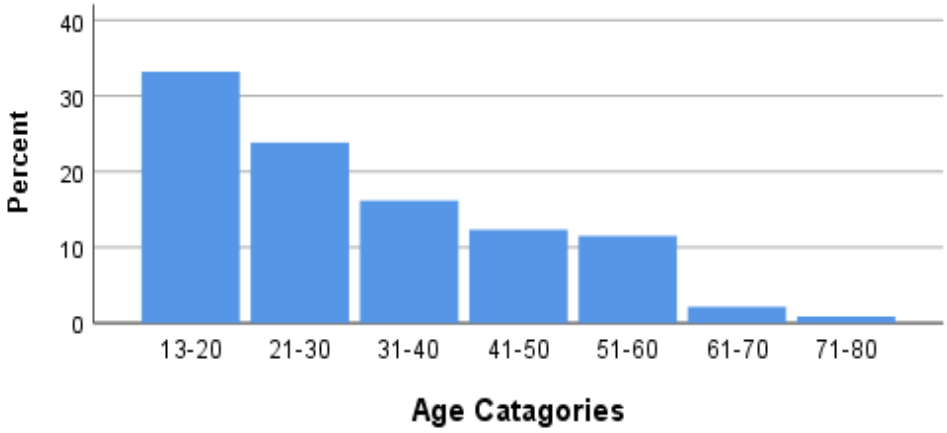

Figure 2: Proportion of patients from different age catagories

There is a male predominance with a total of 144 (61.3 %) males and 91(38.7%) females with a M: F ratio of 1.58.

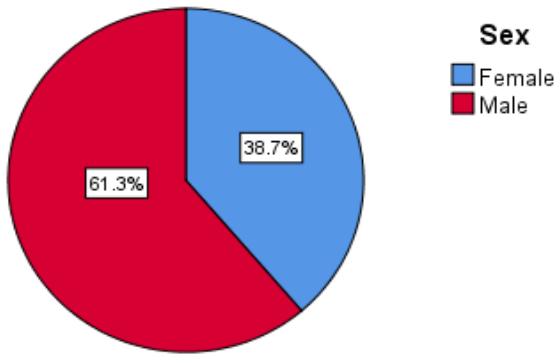

Figure 3: Sex distribution of acute leulemia patients

When we see regional distribution, 83(35.3%) of patients came from Oromiya, 53(22.6%) came from the capital city Addis Ababa, 43(18.3%) came from SNNPR, 36(4.3%) from Amhara and 10(4.3%) came from Tigray regions in respective order. There was no patient who came from Benishangul-Gumuz region.

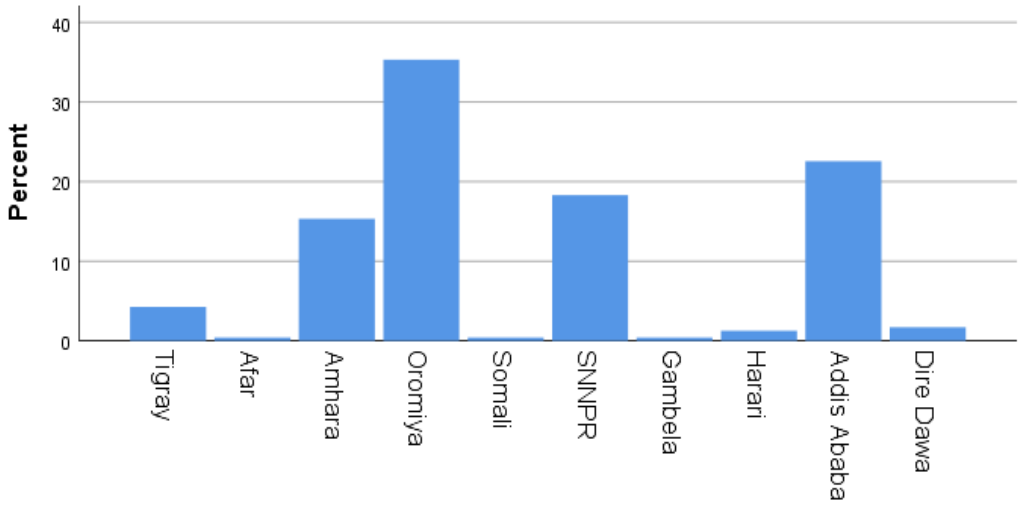

Figure 4: Proportion of patients from different regions

The most common presenting symptom was symptoms of anemia, which 221(94%) of patients had. Followed by symptoms of infection found in 127(54%), constitutional symptoms in 123(52.3%), bleeding in 114(48.5%) of the patients. Bone pain was found in 21(8.9%) and symptoms of meningeal inflammation in 6 (2.6%) of patients only. Among the sub-types patients with AML M3 (APL) has increased chance of presenting with bleeding, among whom 15(75%) had bleeding during presentation.

The duration of illness at the time of presentation ranged from 1 week to 32 weeks. The mean duration of illness at presentation was 7.45 weeks (SD±5.8). The median duration of illness was 6 weeks. Almost three fourth of the patients (74.5%) presented with symptoms of 8 weeks duration or less.

With regards to physical signs, pallor was the commonest and was found in 210(89.4%) of patients. Lymphadenopathy (LAP) was seen in 99(42.1%), splenomegaly in 80(34%), fever ≥38 ^{0}C in 72(30.6%), sternal tenderness in 37(15.7%), mucocutaneous bleeding in 34(14.5%), hepatomegaly in 25(10.6%) of the patients. The rare physical findings were gum hypertrophy which was present in 9(3.8%), suspicious myeloid sarcoma in 7(3%) and meningeal signs in 2 (0.9%) of the patients.

ALL patients had more frequency of having LAP and splenomegaly, 53.2% and 50% compared with AML patients who had LAP and splenomegaly in 34.5% and in 23% of the patients respectively. Spleen size ranged between 1 and 20 cms, with a median of 6 cms and mean of 6.53 cms (SD±3.8).

Symptoms	Percentage	Signs	Percentage
Symptoms of anemia	*94%*	Pallor	89.4%
Symptoms of infection	*54%*	Lymphadenopathy	42.1%
Constitutional symptoms	*52.3%*	Splenomegaly	34%
Bleeding	*48.5%*	Fever≥38^{0}C	10.6%
Bone pain	*8.9%*	Sternal tenderness	15.7%
Meningismus	*2.6%*	Mucocutaneous bleeding	14.5%
		Hepatomegaly	10.6%
		Gum hypertrophy	3.8%
		Myeloid Sarcoma	3%
		Meningeal signs	0.9%

Table 1: Common presenting symptoms and signs in patients with acute leukemia

The most common laboratory finding was anemia which was present in 96.2% of the patients followed by thrombocytopenia which was found in 94.9%. From the lab parameters, hemoglobin (Hgb) levels ranged between 1.7 g/dl to 16.5 g/dl with a mean Hgb level of 6.7g/dl (SD ±2.56). Platelet count ranged between 0-318,000cells/ µl with a mean of 47,105.9 cell/µl (SD±51587.6) and median of 29,000 cell/µl. Total WBC count raged from 330cells/µl- 620x10^3cells/ µl. The mean WBC count was 57,106 cells/ µl (SD±80,666) and median was 28,180 cells/ µl. From the total patients 152 (64.6%) had leukocytosis, 49(20.9%) had leukopenia and 34(14.5%) of patients had normal WBC counts. About 50(21.3%) of patients had WBC count >100x10^3/µl.

The serum LDH level ranged from 188 IU/ml to 12,000 IU/ml with a median value of 876 IU/ml. The serum uric acid ranged between 3mg/dl and 21.2mg/dl and the median is 5.3mg/dl. The serum creatinine ranged between 0.5mg/dl and 5mg/dl with a median of 0.9 mg/dl.

Comparing the lab values patients with ALL have a slightly higher mean levels of uric acid, LDH and creatinine. Likewise, the spontaneous TLS rate is higher (12)12.8% in ALL patients compared with AML which is which is 5(3.6%).

When we see the peripheral morphology and bone marrow findings, the median peripheral blast count was 57% and mean was 52.9% (SD±29) whereas the median bone marrow blast count was 80% with a mean of 70.35%(SD± 24.1).

With regards to the mode of the diagnosis majority of the patients, 189(80.4%) had only morphological diagnosis. About 42(17.9%) were diagnosed by combining morphology and flow cytometry whereas 3(1.3%) were diagnosed with morphology and cytogenetics. One patient had all three modalities done.

Among the FAB subtypes of AML, M4 is the commonest subtype accounting for 34(24.5%) of patients, followed by M1 and M2 accounting for 21(15.1%) each. AML M3 (APL) was found in 20(14.4%) of patients ranking fourth, M5 subtype is seen in 16(11.5%) and M0 in 11 patients (7.9%). M7 subtype was diagnosed only in 2 patients. None of the patients were diagnosed with M6 or erythroid leukemia. For the rest of 14 patients FAB subtyping was not specified.

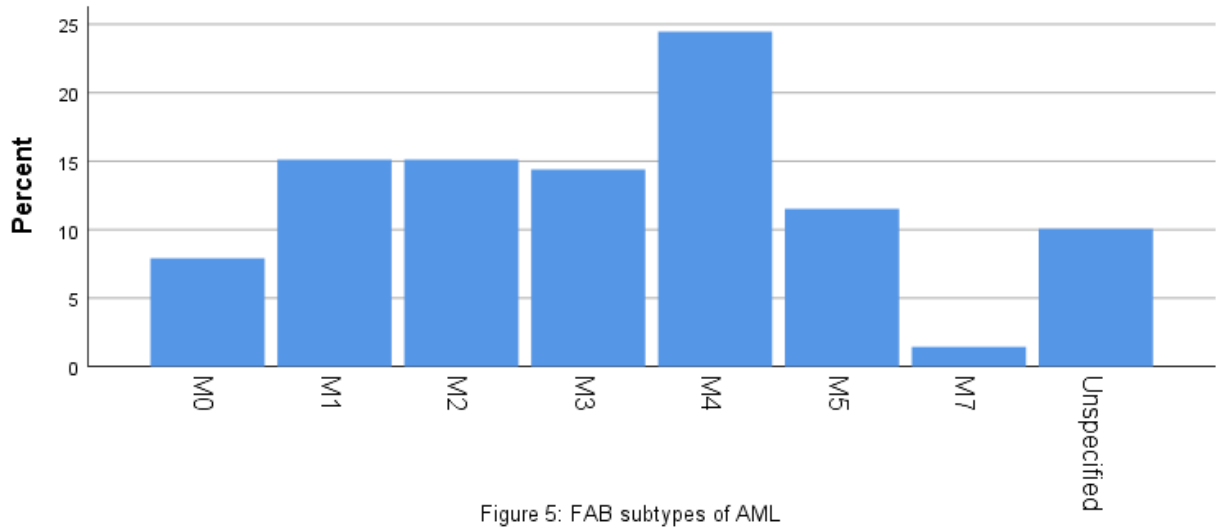

Figure 5: FAB subtypes of AML

Among ALL patients 49(52.1%) were subtyped to L2 subtype, 7(7.4%) to L1 subtype and 3(3.2%) to L3 subtype. 35(37.2%) patients did not have subtyping done. Among the 13 ALL patients who had diagnosis with flow cytometry, 9 patients had pre-B cell ALL, 2 patients had mature B-ALL, 2 other T cell ALL.

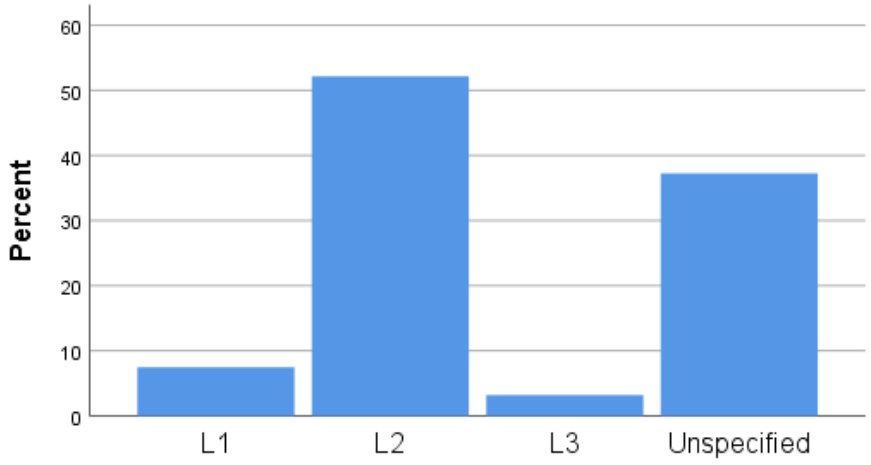

Figure 6: FAB subtypes of ALL

With regards to the prevalence of concomitant comorbidities, 3(1.3%) patients were HIV positive, 9(3.8%) were HBV positive, 1 (0.4%) was positive for HCV, 4(1.7%) patients had established cardiac disease, 8(3.4%) patients had diabetes mellitus, 9(3.8) patients had hypertension, whereas 7(3%) were diagnosed to have concomitant TB and put on anti-TB. Other less prevalent comorbidities were seizure disorder, CLD and bronchial asthma.

Regarding treatment status, among all patients 99(42.1%) received cyto-reductive agents. 109(46.4%) of patients did not start any type of chemotherapy. These patients either died or went against medical advice before starting chemotherapy. The rest of 126(53.6%) of patients were started on some type of chemotherapy. Among these 16(12.7%) patients took palliative treatment only while 110(79.3%) took intensive induction regimens. Among the 110 patients who took intensive induction regimens 66(60%) patients completed intensive induction, 13(11.8%) defaulted during the induction phase whereas 31(28.2 %) died during induction.

The average day of starting chemotherapy after bone marrow result was day 19.95(SD±27.6) and the average day of starting chemotherapy after admission was on day 15.4(SD±12.). The median

dates starting chemotherapy after bone marrow result acquisition and admission were 12th day and 13th day respectively. This was lower in patients with AML M3 with average chemotherapy start date of 9.6(SD±10.2) after bone marrow result and average chemotherapy start date of 6.13(SD±9.4) after admission. The median dates were 3rd day and 5th day which shows AML M3 patients started chemotherapy earlier than other patients.

Among 55 ALL patients who was started on chemotherapy 51(92.7%) took the CALGB regimen as an induction regimen, 2(3.6%) took CALGB and Imantinib, one patient took 7+3 regimen first then CALGB after diagnosis was revised following flow cytometry. One patient was given palliative therapy alone.

Among patient 58 patients with non-M3 AML 43(74.1%) took 7+3 regimen, 1 patient took 5+2 regimen, 15(25.8%) took palliative therapy only. Among a total of 20 APL cases 11 patients took chemotherapy. 3(27.2%) took ATRA only, 3(27.2%) others took ATRA+ATO and 5(45.6%) took ATRA+ other chemotherapy. One patient who had bi-lineage took 7+3 regimen.

With regards to the course of induction, for one patient the details of the information were not available as he took induction in other set up. However, among the rest 85(78 %) were given induction chemotherapy continuously without interruptions whereas in the 24(22%) patients there was at least one interruption during induction. Among these patients 106(97.2%) had complications following induction chemotherapy. The commonest complication in the post induction period was neutropenic fever which complicated the hospital course of 103(96.2%) patients, followed by bleeding into vital organs (DAH, ICH and retinal hemorrhage) which occurred in 16(15.1%) of patients, severe electrolyte derangement in 19(17.9%), AKI in 9 (8.5%), liver injury in 4 (3.8%) and venous thromboembolism in 3(2.8%) of patients.

Coming to the outcome of treatment, among all patients who took intensive induction regimens 31(28.2%) patients died during induction,12 (10.9%) defaulted, 67(60.9%) of patients completed. From those who completed, remission status was not checked in 8(11.9%) of patients whereas for the 59(88.1%) patients remission status was checked. Of the 59 cases 46(77.9%)

achieved complete remission, 4 (6.8%) had partial remission and 9 patients (15.3%) had resistant disease with no response to therapy.

When response rates are seen separately, patients with AML had CR rates of 63.3% whereas ALL patients had CR rates of 92.9%. However, death before completion of induction is around 40.7% in ALL and 16.6% in AML this could be due to the shorter duration of induction in AML than ALL. The median time of achieving remission was 4 weeks and mean was 4.95 weeks (SD±2.19).

With regards to post-remission therapy 20 AML and 20 ALL patients took at least one round of consolidation therapy.

Coming to burden of mortality, there were a total of 104 (44.3%) confirmed in-hospital deaths. Of these patients 53(51%) died before starting chemotherapy, 31(29.8%) died during induction, 6(5.8%) died post induction after achieving CR, 4(3.8%) died after post induction with no response, 7(6.7%) died post induction with unknown status, 3(2.9%) died while on palliative therapy.

The date of death post first admission ranged from 2nd day- 97th day, with average date of death being 23rd day. The commonest cause of death was neutropenic sepsis which accounts for the death of 45(43.3%) of total deaths, followed by intracranial hemorrhage in 16(15.4%), non-neutropenic sepsis in 11(10.6%), DAH in 9(8.7%), leukostasis in 9(8.7%), PTE in 4(3.8%), liver failure in 2(1.9%) and 1 patient died of sudden cardiac arrest. There was no sufficient information on the cause of death for 7 patients.

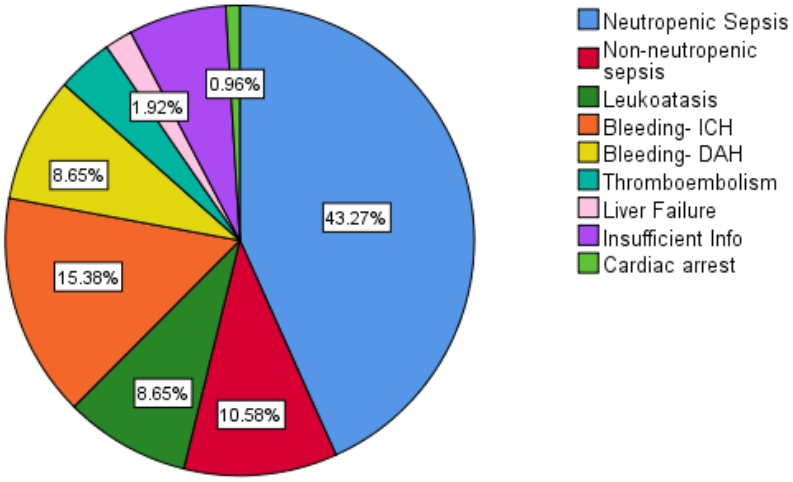

Figure 7: Causes of death in patients with acute leukemia

Apart from the 104 patients who are confirmed to have died in this hospital, out of the 131 remaining 68 (51.9%) went against medical advice from the inpatient wards, 8(6.1%) disappeared from in patient ward without notice, 42(32.1%) lost from hematology clinic after being given appointments, 6 (2.6%) were referred abroad for better treatment, 1 patient referred to private setup for mechanical ventilation outcome remains unknown.

Among 49 patients who achieved remission and survived the immediate post induction phase 16 patients relapsed. 2 patients within 3 months of remission, another 2 patients within 3-6 months following remission, 7 patients relapsed between 6 months and 1 year following remission, 3 patients between 1-2 years post remission, and 2 other relapsed beyond 2 years of initial remission. The rest 27 patients discontinued follow up or relapse status is not known. Whereas 6 patients are still alive and on follow up without relapse.

Among the 6 alive patients 3 are ALL and 3 are AML. Their duration of outcome measures ranges from 22 to 53 months. The one with 53 months EFS is a patient with APL.

7. Discussion

This study included the largest number of acute leukemia patients compared with previous studies done in Ethiopia. The study published by Shamebo on Ethiopian Medical Journal in1994 reported 88 patients within a period of 10 years.[11] With regards to estimated average number of patients seen per year, the study from University College Hospital, Ibadan, Nigeria, also reported average of 10 acute leukemia per year which is very small compared with 78 patients/year estimate seen at our center according to the findings of this study.[12] This number is even believed to be an underestimate as there are significant medical record charts lost from the central medical record store. This high number is believed to be from the effects of referral from all centers in Ethiopia as TASH is the only center in the whole country with relatively comprehensive acute leukemia care.

From a total of 235 patients with acute leukemia AML makes up 59.1% followed ALL around 40%. The proportion of AML in this study was slightly higher than the previous study by Shamebo done in TASH which reported AML to be 53.7% and ALL 46.3%. [11] A study from University College Hospital, Ibadan, Nigeria showed AML proportion of 56 % where as a study from Agakhan University Hospital, Nairobi Kenya reported a 67% of AML and 31.8% of ALL.[12,13] Similarly, studies from St. John's Medical College Hospital, Bangalore, India and University Hospital of Marrakech, Morocco also reported a higher proportion of AML which were 56% and 54.47% respectively. Generally, adult and adolescent studies show that AML is more prevalent than ALL.[14,15]

The age of patients ranged between 13 -76 similar with the 1994 study by Shamebo which reported age range of 13-78 years. The mean age was however higher, 32 years compared with 29.6 which was reported in that study.[11] The median age for AML patients alone was 32 which was lower than the value reported from Institute of Medical Sciences, India which was 35.[16] The other studies from St. John's Medical College Hospital, India and University Hospital of Marrakech, Morocco reported a higher mean age values of 41 years and 47 respectively.[14,15] With regards to the age proportion the majority of the patients in our study belonged to age categories 13-20 followed by 21-30 which shows a younger population is affected compared with the findings reported from university hospitals in India and Nigeria which found the peak

age to be 41-50 years.[12,16] This finding might even be younger compared with European and US figure reported on most literature. This shows that our patients are much younger than other set ups. But generally we found that the proportion of ALL significantly decreases as age increases, with 85% of patients with ALL presenting younger than age of 40.

Regarding sex distribution there was an absolute male dominance with a total of 144 (61.3 %) males and 91(37.3%) females with a M: F ratio of 1.58. This value was higher than most findings from other sites. For example, the findings from two studies in India reported M: F ratio of 1.2:1, the study from Morocco which reported 1.05 and also 1.03:1 reported by the Agakhan University Hospital in Kenya.[13,14,15,16] The reason for this could be hypothesized as a higher risk of exposure to carcinogens in males such as fertilizers during farming or due to a poor health seeking capacity of females in Ethiopia, or any other reason should be looked into in the future.

In our study, the most common presenting symptom was symptoms of anemia, which was found in 94%. Similarly, the study done in University Hospital of Marrakech, Morocco showed symptoms of anemia was the commonest presenting symptom which was present in 73% of patients.[15] In contrary, according to the findings of the study from St. John's Medical College Hospital, fever was the commonest presenting symptom. [14]

However, another study done in India on AML patients showed anemia was the commonest presenting symptom. In this study, 54% of patients also had symptom of infection during presentation. This was similar to the finding from Morocco which reported 52%. [15] With regards to the presence of infection during presentation, rate as high as 81% was reported from a study done in AML patients in Pakistan. [17] Regarding bleeding, 48.5% of our patients had bleeding and this was very high compared with the 24% reported by St. John's Medical College Hospital, India. [14]

Coming to physical signs, pallor was the commonest and was found in 89.4% of patients. This was also depicted on Indian studies. [14,16] In our study 42.1% of patients had LAP which was higher than 28% reported from India. Similarly, splenomegaly was reported in 34% and is higher than the 30% reported from the same study. Lymphadenopathy and splenomegaly were seen more commonly in ALL than AML in our study which was similar to the study from St. John's Medical College Hospital, India. However, the absolute proportion of AML patients having LAP

and splenomegaly was much higher than what most studies have reported.[16] This could be due to a higher proportion of monocytic variant of AML(M4) which are known to result in tissue infiltration. This could also be due to a higher prevalence of disease conditions like tuberculosis, malaria, leishmaniosis and schistosomiasis.

Anemia is the most common hematological abnormality found in 96.2 % which was also illustrated on the study by St. John's Medical College Hospital, India.[14] The study from morocco found that 86% of the patients were anemic during presentation.[15] The mean Hgb level of in our study was of 6.7g/dl similar with the findings of Shamebo and it was slightly higher than reported by the AML study from India.[10] The second commonest finding was thrombocytopenia which was evident in 94.9% of patients which was similar with the finding of most studies. Leukocytosis was apparent in 64.6% and this is comparable with the findings of University Hospital of Marrakech, Morocco but higher than the 49% reported by St. John's Medical College Hospital, India.[14,15]

According to our findings, only 7.2% of patients were diagnosed to have TLS and this was much smaller compared with the 80% reported by St. John's Medical College Hospital, India.[14] This could be due to the under diagnosis of biochemical TLS due to inconsistencies in availability of all laboratory tests required for diagnosing TLS in our set up or over diagnosis by the other center. However, the finding that higher mean creatinine and uric acid values were reported in patients with ALL than AML is shared with the findings from other studies.[14]

In most centers, leukemia initially suspected with the presence of abnormality in one or more CBC values. Then, the diagnosis is consolidated by visualization increased blast on peripheral morphology and bone marrow. Concomitantly, flow cytometry and cytogenetic studies are utilized to classify leukemia which has paramount importance to decide on treatment and prognosticate patients. In our study, majority of the diagnosis were made only morphologically. Flow cytometry or cytogenetics were employed in only 19.6% of patients. This was a very small proportion compared with 93% and 95.6% utilization of flow cytometry in the studies from India and Kenya respectively. [13,14]

Among the FAB subtypes of AML, in our study M4 is the commonest subtype accounting for 34(24.5%) of patients, followed by M1 and M2 accounting for 21(15.1%) each. This finding was similar with the study from University Hospital of Marrakech, Morocco. [15] In contrary, two studies from University College Hospital, Ibadan, Nigeria and National Institute of Bone Diseases, Karachi (NIBD), Sind, Pakistan, showed that the M2 subtype was the commonest subtype of AML. This was followed by the M4 on the study from Nigeria and M1 on the study from Pakistan. [12,17] However, a study from Institute of Medical Sciences, India found that the commonest subtype was M3 which was seen in 25% followed by M2 and M1.[16]

The commonest ALL subtype in our study was L2 followed by L1 and L3 in consistent with the finding reported from University College Hospital, Ibadan, Nigeria which showed among all case of ALL, 68% were diagnosed as L2-subtype and only 9% were diagnosed as L3 i.e. (L2>L1>L3).[12] Even though only few patients had flow cytometry done in our study, the pre-cell ALL was the commonest subtype similar to the finding in Morocco and Kenya. [13,15]

Regarding, the time of chemotherapy initiation, the median average day of starting chemotherapy after bone marrow result and admission were 20^{th} and 15^{th} day respectively which is very long keeping the urgency of the disease into account. This delay may have been created by the delay of requesting bone marrow and waiting for the result from pathology department. The time was shorter for AML M3 patients which was 10^{th} and 6^{th} day after bone marrow result and admission date respectively. This again is very long when compared with top-urgent nature of this particular subtype.

With regards to treatment outcome, patients with AML had CR rates of 63.3% which was similar with the report from Institute of Medical Sciences, India which was 63.2% but much higher than the 6.2% reported by Shamebo in TASH 25 years ago. [10,16] An old study from Kenya in 1989 showed rates of 54%. [11]When remission rates of AML M3 was seen separately among the 3 patients who complete induction all achieved remission. However, there was 50% death during induction which was more than double the figure reported from India. [16]

ALL patients had a markedly higher CR rates of 92.9% which significantly excels the 38.4% reported by Shamebo.[10] This finding were comparable with the finding of the brazil which reported 93% CR rate with GMALL protocol. However, the overall survival in the Brazil study

was 41% which is very high than the findings from our study which is assumed to be around 3.2%.[18] An old Kenyan study which had younger patients also showed CR rates of 87%. [11] A study from Chicago comparing the efficacy of CALGB and CCG protocol reported a CR of 90% from both wings. [19] Findings of comparative studies on the outcome ALL treatment from well-developed countries show that a very high success rates can be achieved with pediatric protocols. Studies from Finland and Sweden CR rates of 96 and 99% with pediatric protocols.[20,21] However, most studies from this set also showed much higher 5 years over all event free survival.[19,20,21]

Even though the CR rates in our set up are found to be comparable with most centers from different countries, our finding show that there is a very high induction and pre-induction death rates. This could be from very poor supportive care such as infection control, proper use of potent antibiotics, sub-optimal transfusion service and ICU care.

Our study also showed that loss of follow up from both in-patient and out-patient department was very high. This could be from poor patient and family awareness about the patient's condition, poor financial capacity to afford the cost of treatment and inconvenience created by long distance of the center from patient's area of residence which makes adherence to the treatment of leukemia which commonly requires prolonged in-patient stay and follow up difficult for most patients.

8. Conclusion

In, conclusion the clinical presentation of patients with acute leukemia in our set up is similar with most centers. However, more young patients are affected. Male predominance seems to be a bit exaggerated from other reports. Significant number of patients either die or go against medical advice before starting chemotherapy. The rate of CR particularly in ALL patients is comparable with most centers. However, there is a very high induction and post induction mortality. The majority of patients die from neutropenic fever and bleeding.

9. Recommendation

Limitations of acute leukemia treatment in developing countries in general are various. Solving these complex limitations need time as well as dedicated hospital administration and coordinated support from higher governmental bodies like FMoH. Interventions should be tailored to each limitation at each level to improve the quality of acute leukemia care.

Better hematologic diagnostic modalities such as flow cytometry and cytogenetics should be made available for prompt diagnosis and early treatment. Improved urgency of making bone marrow results available early would also hasten the initiation of treatment of acute leukemia. These can be achieved in collaboration with the department of Pathology in TASH. The availability of other laboratory modalities like coagulation profiles, organ function test and serum electrolytes and microbiological tests should be made consistent and sustained.

Further prospective studies are needed to identify the gaps to identify the incriminated gaps for the very high pre-induction and induction mortality of patients. As neutropenic fever was found to be the number one killer in acute leukemia patients according to our findings, prompt measures should be done to improve the infection control strategies in acute leukemia wards. Wards specialized for acute leukemia care with reverse isolation and limited visitors are known to improve this. This need a very prompt and decisive action from both the administration of the hospital and FMoH.

In addition, better ICU set up with a better infection control practice should be placed to support those patients in need. With regards to tackling the second most common cause of death, i.e. bleeding availability of blood and blood products should be improved in collaboration with the national blood bank.

The causes for the very high loss of follow up rate should also be identified. Public awareness creations should also be worked on. Decentralization of Hemato-oncology services to regional hospitals might improve patient comfort and adherence to treatment.

Specific to AML patients, the long term survival without subsequent hematopoietic stem cell transplant remain very low. Therefore, it is rational to recommend to establish this service at least at TASH the center which serves a large number of acute leukemia patients from all over the country.

10. Strengths and Limitations of the study

The strength of this study, the fact that it tried to study a disease condition which is very common especially in the center where the study was conducted, i.e. TASH, but the least studied area for many years.

It also involved a large number of patients and tried to describe the details of clinical presentation as well as treatment out comes. It also tried to identify how the clinical profile and presentation of patients' is different from other set ups. The scope of the study was so wide that some of the details of data, particularly on neutropenic fever were not included in this paper. However, these will be revealed on subsequent papers which would add more to the knowledge that is already bestowed with the finding of this study.

Finally, the study also gave a clue on possible limitations of acute leukemia care specifically in TASH which might be used as a stepping stone for further study aimed at identifying specific gaps.

Coming to the limitation, the major limitations of the study was the fact that it was impossible to enroll all cases as there was difficulty of accessing the medical record chart of significant number of patients due to a poor storage and retrieval system at the hospital. It also did not include those patients who might have been diagnosed at emergency department and never been admitted to the Internal Medicine wards. This might have underestimated the number of acute leukemia patients admitted and treated at the center.

The other limitation of the study is as it is a retrospective study, there was few missing information particularly on some of the laboratory parameters such us uric acid and LDH, exact date of bone marrow result acquisition and the like.

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Annexes

Annex 1

Data collection protocol for the Study of Patients with Acute Leukemia (AL) at the TASH

Serial No: _____ Chart Number (MRN): _____

A. Demographic data:

Initial: _____ Region: _____

Age: _____ Sex: _____

Date of Admission-: _____

Date of AL diagnosis (BM report date): _____

B. Presenting symptoms:

B1Presence of infection during presentation:	1. Yes	2. No	3. Unknown
B2. Anemia symptoms:	1. Yes	2. No	3. Unknown
B3. Bleeding tendencies:	1. Yes	2. No	3. Unknown
B4. Bone pain:	1. Yes	2. No	3. Unknown
B5. Constitutional symptoms	1. Yes	2. No	3. Unknown
B6. Symptoms of meningismus:	1. Yes	2. No	3. Unknown

C. Duration of illness (in weeks): _____

D. Presenting signs:

D1. Fever $\geq 38^0$C:	1. Yes	2. No	3. Unknown
D2. Pallor:	1. Yes	2. No	3. Unknown
D3. Mucocutaneous bleeding:	1. Yes	2. No	3. Unknown
D4. Lymphadenopathy:	1. Yes	2. No	3. Unknown
D5. Raised JVP/S3 gallop/ Peripheral edema	1. Yes	2. No	3. Unknown
D6. Splenomegaly:	1. Yes	2. No	3. Unknown

D7. If yes for splenomegaly, size in CM BLCM:_____

D8. Bone (sternal) tenderness:	1. Yes	2. No	3. Unknown
D9. Meninigeal sign/impaired consciousness:	1. Yes	2. No	3. Unknown

D10. Other, specify: _____

E. Laboratory findings at presentation:

E1. WBC (/μL):_____

E2. Hb (g/dL): _____

E3. Platelet count (/μL):_____

E4. Peripheral blast count (%) _____

E5. Bone marrow blast count (%) _____

E6. LDH(IU): _____

E7. Uric Acid(mg/dL): _____

E8. Creatinine (mg/dL): _____

E9. Tumor lysis syndrome (according to Cairo Bishop Criteria) 1. Yes 2. No 3. Unknown

F. With which morphologic type of leukemia was the patient diagnosed?

1. ALL 2. AML 3. Unclassifiable

G. If ALL, which subtype according to FAB?

1. L1 2. L2 3. L3 4. Not specified

H. If AML, which subtype according to FAB

1. M0 2. M1 3. M2 4. M3 5. M4 6. M5 7. M6 8. M7 9. Unspecified

I. Which modality was used for diagnosis?

1. Morphology alone
2. Morphology with Immunophenotyping by flow cytometry
3. Morphology with Cytogenetic Analysis
4. Morphology with Immunophenotyping and Cytogenetic Analysis

J. If Immunophenotyping by flow cytometry done in ALL, the type is:

1. pre-B ALL 2. pre T-ALL 3. Mature B-ALL 4. Bi-lineage 5. Bi-phenotypic

K. If cytogenetics done, the result is: _____

L. Comorbid condition at presentation?

L1. HIV	1. Yes	2. No	3. Unknown
L2. hepatitis B	1. Yes	2. No	3. Unknown
L3. hepatitis C	1. Yes	2. No	3. Unknown
L4. Cardiac disease	1. Yes	2. No	3. Unknown
L5. Diabetes	1. Yes	2. No	3. Unknown
L6. Hypertension	1. Yes	2. No	3. Unknown

L7. Other, specify: _____

M. Status of treatment

A. Did not start Chemotherapy
B. Defaulted
C. Completed standard Induction
D. Died during induction
E. Palliative treatment

N. If chemotherapy was started

N1. How many days after diagnosis (BM report day) started? _____

N2. How many days after hospital admission started? _____

O. Was Cytoreductive therapy given to patients with high WBC count before induction chemotherapy?

1. Yes 2. No 3. Unknown

For ALL patients only (The two questions bellow - P and Q)

P. Initial treatment (regimen) given to ALL:

1. CALGB
2. Imatinib with chemotherapy
3. Palliative treatment
4. Other regimen, specify: _____

Q. In ALL patient with Complete Remission, which regimen was used for consolidation?

1. Continued on as per CALGB's protocol
2. Other(specify)_____

For AML patients only (The two questions bellow- R and S)

R. Initial treatment (regimen) given to AML:

1. 3+7
2. ATRA
3. ATRA+ chemotherapy
4. ATRA+ATO
5. Palliative treatment
6. Other regimen, specify: _____

S. In AML patient with Complete Remission, which regimen used for consolidation?

1.5+2 regimen
2. High dose cytarabine
3. ATRA/ATO/Chemotherapy
4. Other(specify)_____

For all Patients

T. Was treatment given continuously without interruption?

1. Yes 2. No

U. Was there any complication noted during induction?

1. Yes 2. No

V. What complications were noted during induction (multiple answers possible)?

1. Neutropenic fever
2. Bleeding to vital organs
3. Severe electrolyte derangement
4. Renal failure

5. Liver Injury
6. Venous thromboembolism
7. Other, specify _____

W. What was the outcome of induction?

1. Achieved Complete Remission
2. Achieved Partial Response
3. Achieved No response
4. Defaulted
5. Died during induction
6. Unknown

X. If the patient achieved Complete Remission, time taken to achieve CR in weeks: _____

Y. If the patient died:

AIV1. At what day post admission? _____

AIV2. At which course therapy and status of the patient during death?

1. Died before chemotherapy
2. Died during induction
3. Died after achieving complete remission
4. Died after induction with no response
5. Died after induction with unknown status

Z. What was the presumed cause of death?

1. Neutropenic sepsis
2. Non-neutropenic sepsis
3. Leukostasis
4. Intracranial Hemorrhage
5. Diffuse Alveolar Hemorrhage
6. Progression of disease
7. Thrombo-embolism
8. Liver failure
9. Chemotherapy toxicity related to impaired renal function
10. Bowel obstruction
11. Summary of deaths Unknown (Insufficient Information)

AI. Did the patient relapse after achieving complete remission?

1. Yes 2. No 3. Not Known/ Discontinued follow up

BI. If relapsed, when did he/she relapse?

1. Within 3 months
2. 3-6 months
3. 6months to 1 year
4. 1 year- 2 years
5. Beyond 2 years

CI. If the patient is currently alive,

AIII1. Duration of outcome measures (in months) _____

AIII2. What is his/her final condition/ final information about the patient?

1. Alive with maintained CR
2. Alive without achieving remission
3. Alive with relapsed disease
4. Lost to follow-up during OPD appointments
5. Went against medical advice from inpatient wards
6. Disappeared from ward without notice
7. Referred abroad
8. Other, specify: _____

NEUTROPIC FEVER QUESTIONS

A. Did the patient have infection during his/her stay,
   1. Yes 2. No

B. If yes, how many episodes did he/she have? _____

C. Where were presumed focuses of Neutropenic fever (multiple answer is possible for recurrent infection?)
   1. Chest 2. GI 3. Urinary 4. Skin 5. Other (specify) 6. Not localized

D. What were the types of Infection? Multiple answers possible
   1. Primary septicemia 2. Pharyngitis Skin & soft tissue infection 3. Pneumonia
   4. Anal & rectal abscess 5. Urinary tract infection 6. Typhilitis
   7. Thrombophlebitis 8. Peritonitis 9. Fungal infection
   10. Others, specify _____

E. Was culture taken during neutropenic fever?
   1. Yes 2. No 3. Unknown

F. If yes, what was the result?
   1. Positive Growth (specify isolated organism) _____
   2. No Growth

G. Was the patient started on antifungal therapy empirically?
   1. Yes 2. No

Annex 2

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome

Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
T-lymphoblastic leukemia/lymphoma

Annex 3

The Cairo Bishop Criteria of Tumor Lysis Syndrome

Element	Value	Change from baseline
Uric acid	≥476 micromol/L (8 mg/dL)	25% increase
Potassium	≥6.0 mmol/L (or 6 mEq/L)	25% increase
Phosphorus	≥2.1 mmol/L (6.5 mg/dL) for children or ≥1.45 mmol/L (4.5 mg/dL) for adults	25% increase
Calcium	≤1.75 mmol/L (7 mg/dL)	25% decrease
NOTE: Two or more laboratory changes within three days before or seven days after cytotoxic therapy.		

The Cairo-Bishop clinical tumor lysis syndrome definition and grading

Complications	Grade					
	0	1	2	3	4	5
Creatinine	≤1.5 x ULN	1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 x ULN	Death
Cardiac arrhythmia	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with HF, hypotension, syncope, shock)	Death
Seizure	None	-	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death