Clinical Characteristics, Treatment, Outcome and Associated Factors of Acute Lymphoblastic Leukemia Patients Admitted to Hematology ward of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia 21 Months Prospective, Observational and Cross Sectional Study

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Abbreviation

AAU……..Addis Ababa University

AL……..Acute Leukemia

ALL……..Acute Lymphoblastic Leukemia

AML……..Acute Myeloid Leukemia

AYA……Adolescents & Young Adults

BC……Breast Cancer

BLCM……Below Left Coastal Margin

BM……..Bone Marrow

CALGB……..Cancer and Leukemia Group B

CBC……Complete Blood Count

CC……Colon Cancer

CNS……Central Nervous System

ECOG……Eastern Cooperative Oncology Group

EGIL……European Group for the Immunological Characterization of Leukemias

FAB……French-American-British

FC……..Flowcytometry

FMoH……..Federal Ministry of Health

GI……..Gastrointestinal

GVHD……..Graft Versus Host Disease

Hb……..Hemoglobin

HIV……Human Immune-deficiency Virus

HSCT……Hematopoietic Stem Cell Transplantation

IHC……Immunohistochemistry

JVP……Jugular Venous Pressure

LDH……..Lactate Dehydrogenase

LIC…….Low Income Countries

LP……Lumbar Puncture

MRN…….Medical Record Number

NCD……..Noncommunicable Disease

TLS…….Tumor Lysis Syndrome

TASH……Tikur Anbesa Specialized Hospital

UK……..United Kingdom

USA……..United States of America

WHO……World Health Organization

WBC…….White Blood cell

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Abstract

Background: Acute lymphoblastic leukemia is one of the commonest referral diagnoses to TASH. Due to need of urgent diagnosis and treatment, there is currently a need to improve the service given to manage this type of leukemia. Patients treated for ALL in this center have usually poor outcome. There is a need to identify the gap in diagnosis and management of this disease and this study aims to fill that gap.

Objective: The primary objective of this study is to assess the outcome and its associated factors among adult ALL patients admitted to hematology ward of TASH.

Methods and materials: This is a prospective, cross sectional and observational study that was conducted on ALL patients admitted to hematology ward of TASH. The study period was from January 01/2023 to September 30/2024.

Result: a total of 174 ALL patients were admitted to hematology ward of TASH from January 1/2023 to July 31/2024. 101 (58%) were males and 73 (42%) were females. M: F ratio was 1.4. The age range of patients was from 15 years to 78 years. The mean age was 31.4 (SD ± 14.74), the median was 28. The most common presenting symptom was symptoms of anemia, which were present in 92% of patients. Constitutional symptoms (70.1%) and fever (53.4%) were the next common symptoms. Pallor was the commonest sign seen in 87.4% of patients. LAP and splenomegaly were seen in 43.1% and 37.4% of patients respectively. The mean WBC count was 58, 760 (SD ± 87,059). The mean hemoglobin level was 7.71g/dl (SD ±3.025) and the mean platelet count was 60,736 (82,969 ± 82,960). 19 patients have t (9,22) positive.112 (64.4%) of patients were started on induction CHT and 74 (66%) achieved CR. The most commonly induction regimen was CALGB 10403. 14 (8%) of patients were started on palliative therapy. On the final data cut of date, September 30/2024, 36 patients were alive and there were 86 documented deaths. The most common cause of death was sepsis and septic shock. This was the cause of death in 83.7 of cases.

Conclusion: ALL is a common referral diagnosis to TASH with clinical signs and symptoms similar with reports from other studies. Treatment results were notable for low CR rates; high induction mortality and frequent loss from followup.

1. Introduction

Acute leukemia is a clonal neoplastic disorder characterized by the proliferation and accumulation of immature and malignantly transformed cells in the bone marrow and peripheral blood. There are two types of acute leukemia. Acute myeloid leukemia (AML) and acute lymphoid leukemia(ALL). (1)

These are rare types of malignancies. According to GLOBOCON, leukemia was the 15th most commonly diagnosed cancer and 11th leading cause of cancer related mortality world wide in 2018. There were 437,033 acute leukemia cases diagnosed in 20118 and 309,006 deaths attributable to acute leukemia (2).

The two types of leukemia are different in their incidence, age distribution and clinical manifestation. AML is more common in elderly while ALL is the most commonly diagnosed acute leukemia in children. The age adjusted incidence of AML is 4.3 per 100,000 annually in USA. Incidence increases with a median age at diagnosis of 68 years in the US (3). For ALL global incidence report showed tha the highest incidence is in the south and Central America countries. For example incidence rates of 2.8 and 3.3 per 100,000 for males and females respectively reported in Ecuador. The other countries in this region reported similar figures. Costarica (2.4 and 2.3 per 100,000) and Colombia (2.3 and 2.1 per 100,000). This countries may have similar sociodemogrophic character to other low and middle income countries (4).

Globally the incidence of leukemia is higher among males than females. 1n 2018, the age standardized incidence rate for males was 6.1 per 100,000 compared to 4.3 per 100,000 for females. Mortality was also higher in males. That is 4.2 per 100,000 for males and 2.8 per 100,000 for females. (2).

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. 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. (6,7).

There is no well documented data regarding to incidence and burden of acute leukemia in Ethiopia. A retrospective study done at TASH reported that a total of 235 acute leukemia patients were admitted to the hospital hematology ward between January 1, 2015 and December 31, 2017. 135 (59.1%) of patients were diagnosed with AML and 94 (40%) diagnosed with ALL. The mean age of patients in that study was 32 years. 61.3% of patients were males and 38.7% were females. (5)

The diagnostic modalities and treatment for acute leukemia requires a very sophisticated set up. The outcome of this disease is highly heterogeneous due to this main factor. In high income countries where the health care system is equipped to deal with this deadly disease, the outcome the outcome is better. In contrast, in lower and middle income countries, where the health system is already stretched with communicable diseases, the outcome is poor (9). In the above mentioned study, from the total of 235 patients, 109 (46.4%) didn't start any kind of chemotherapy. 126 (53.6%) of patients were took

chemotherapy. From this, only 66 (60%) of patients completed the induction treatment. 31 (28.2%) were died and 13 (11.8%) defaulted before completion of treatment (5).

Ethiopia has an estimated population of >100million, and most (84%) live in rural areas. According to WHO projections, low and middle income (LMIC) countries will bear two-thirds of the cancer burden in 2040. The main reasons for the rapid rise in cancer in low and middle income countries are population growth, aging, sociodemographic, and epidemiological transitions (LMICs). The change in the incidence of cancer cases in Ethiopia, on the other hand, was primarily driven by population growth and aging. The stable age-standardized cancer incidence rate suggests that epidemiological and sociodemographic transitions play a minor role in cancer pathogenesis in Ethiopia. In 2019, behavioral risks, metabolic, occupational exposure, and air pollutions were attributed to approximately 20% (17–26%) of cancer in Ethiopia; however, changes in overall risk factors were less than 10% between 2010 and 2019.From 2010 to 2019, the age-standardized rate of cancer death in Ethiopia increased. The findings of this study stand in stark contrast to the age-standardized cancer rates in high-income countries and global trends (12).

Generally, as the above studies demonstrated clearly, there is increasing burden of cancer including acute leukemias in LIC. In TASH, the number of acute leukemia patients referred from all over the country is growing every year. This may be due to the increasing awareness of the burden of acute leukemia among health professionals, especially general internists. The slightly improving economic status of the population may also contribute the willingness of patients and their caregivers to come to TASH and pursue further therapy. Despite this, the service given in the only acute leukemia center in Ethiopia is below par. There are so many gaps in terms of reaching diagnosis, giving the high standard supportive care and specific treatment that should be given to these patients. The problem emanates from both institutional and national health system. The scarcity of resources being the main cause. Now the country MOH focusing on NCD, acute leukemia is one of the disease given more attention to improve the service given. So far, there are only few studies which identify the gaps and most of them are retrospective. This study will assess total burden, clinical characteristics and outcome of acute leukemia in TASH. By doing so, we believe the result of the research will fill information gap and contributes to identify some of the most important problems.

Tikur Anbessa Specialized Hospital is only of specialized hospitals where all of referral cases from all over the country are treated. Acute leukemia is one of the most common referral cases from private and governmental hospitals. Due to this there are large sums of acute leukemia patients who are treated and being treated in our hematology wards. In the past, even though there are few studies conducted to assess the acute leukemia outcome and factors associated with it, we feel there is still a need to do a larger study in order to fill the gap. Previous studies also used smaller sample size. Although acute leukemias are rapidly fatal disease without treatment, this diseases has not given much due attention yet. Being one of the current public health critical issues, which affect the country and the health system in terms of economic, productivity, morbidity and mortality, we believe doing this research will contribute something to enhance the low emphasis given from both the government and community.

2. Research Objective

2.1 General Objective

- To assess the clinical characteristics, outcome and its associated factors among adult ALL patients admitted to hematology ward of Tikur Anbessa Specialized Hospital from January 01/2023 to July 31/2024.

2.2 Specific Objectives

- To assess the demographic profile of ALL patients admitted to hematology ward of TASH from January 01/2023 to July 31/2024.
- To describe the clinical characteristics of ALL patients admitted to hematology ward of TASH from January 01/2023 to July 31/2024.
- To assess the types of treatments given to ALL patients admitted to hematology ward of TASH from January 01/2023 to July 31/2024.
- To determine the outcome of ALL patients admitted and treated at hematology ward of TASH from January 01/2023 to July 31/2024.
- To determine prognostic factors associated with treatment outcome of ALL patients admitted and treated at hematology ward of TASH from January 01/2023 to July 31/2024.

3. Materials and Methods

3.1 Study Design

A prospective, observational, cross sectional, descriptive and analytical study design was used to assess the clinical characteristics and treatment outcome of ALL patients admitted to hematology ward of TASH from January 01/2023 to July 31/2024. The factors which were associated to treatment outcome were also identified and their strength of association with the outcome statistically analyzed.

3.2 Study Area

The study was institution based and conducted at TASH hematology ward. TASH is located in Addis Ababa, the capital city of Ethiopia. The hospital is of the oldest and largest referral hospital in the country with 700 beds. Internal medicine department has around 120 beds. In addition to the inpatient service, internal medicine department has outpatient service organized into different units. Currently this hospital is the only one equipped to treat acute lymphoid leukemia patients in the country. Our research was conducted in C8 and D8 wards. These wards are currently assigned as hematology ward. Patients who were discharged after initial treatment were followed at hematology referral clinic.

3.3 Study Period

Data collection was started on January 01/2003 and ends on September 30/2024. The final outcome of patients was assessed as of September 30/2024, which were the data cutoff date.

3.4 Study Population:

3.4.1 Target population

All ALL patients visited the hematology unit at emergency department or hematology referral clinic.

3.4.2 Study Population

All patients who were admitted to hematology wards of TASH and have confirmed ALL by BM examination were the study population.

3.5 Sample Size

Since acute lymphoid leukemia is a relatively rare disease and the study was an institution based study, we included all available cases. Accordingly, all patients, who were diagnosed to have acute lymphoid leukemia and admitted to TASH hematology ward from January 1, 2023 to July 31, 2024, were included in the study.

3.6 Data Collection

3.6.1 Inclusion criteria:

- All patients with confirmed ALL by BM examination and admitted to hematology ward of TASH.

3.6.2 Exclusion criteria

- Patients suspected to have AML clinically but do not have pathologic confirmation with BM were excluded from the study.

3.6.3 Study variables

<u>Independent variables:</u>

- Demography: Age, sex, Area of residence
- Clinical presentations: Symptoms, signs, CBC profile, Biochemical profile
- Pathologic profile: PM, BMA, Tissue biopsy
- Cytogenetic & molecular studies
- Comorbid conditions
- Type of treatment

Dependent variables:

- Complete remission
- Relapse
- Death
- Overall survival(at time of final data analysis)

3.6.4 Operational definition:

ALL: Morphologically or immunophenotypically (Flowcytometry or IHC) confirmed acute leukemia of lymphoid linage.

B Cell ALL: Immunophentypically (IHC or flowcytometry) confirmed ALL of B - cell linage.

T cell ALL: Immunophenotypically (IHC or flowcytometry) confirmed AL of T-cell origin.

Lymphoblastic Lymphoma: Immunophenotypiclly (IHC) confirmed, from lymph node biopsy, without bone marrow involvement (<25% of blasts in the BM).

CNS disease: >5cells/uL of CSF or positive cytology form cytospin.

Complete Remission (CR): Eradication of all detectable leukemia cells - BM blasts <5% and absent circulating blasts and ANC >1000/uL and Platelet count >100,000/uL with transfusion independence.

Refractory (resistant) disease: Failure 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).

Relapse: after confirmed complete remission, Reappearance of BM blasts >5% and/or tissue based confirmed reappearance of disease.

3.7 Data Collection Process

After permission was granted from the ethical review committee, data was collected from each ALL patient admitted to hematology ward by two internal medicine residents who were part of the research team. Each subject will be asked to give informed verbal consent to participate in the study. Demographic data and symptoms were collected from the patients and/or its attendants. Additional data regarding the symptoms plus signs was retrieved from the patients' medical charts. Laboratory and pathologic results were filled by the data collectors from the investigation papers and laboratory data system. The progress of the patients who were enrolled to the study, followed weekly while they were in the hematology ward and oncology health center. After they discharged from the hospital, follow up was made at hematology referral clinic. To determine their final outcome, in addition to the follow up made at hematology referral clinic, a phone call was made to assess their current and final status. The

data obtained entered directly to a prestructured data collection tool using Kobo tool box data collection software.
As mentioned above, the data was collected by the main investigators and two internal medicine residents. The data was collected for 21 months (from January 01/ 2023 to September 30/ 2024). Data collection supervision was carried out by the main investigator.

3.8 Data Entry and Analysis

Data analysis was made by the main investigator and the research team. Data was entered, compiled and analyzed using Kobo tool box and SPSS version 25. Descriptive statistics was used to summarize demographic, disease characteristics, treatment delivered and outcome of the study population. Bivariable and multi variable Cox regression analyses were applied to investigate determinants the ALL treatment outcome. Survival analysis was done using log rank test and Kaplan Meier curve.

4. Ethical Consideration

Ethical clearance was obtained from the ethical review committee (i.e. the internal review board (IRB) to conduct the study in TASH. Participants gave informed verbal consent before enrollment o he study.

5. Dissemination of research results

After research is completed the main investigator will present the findings to the gathering internal medicine staffs including senior consultants, fellows, postgraduate students and undergraduate students. The research result will be submitted to FMoH and TASH. The published material will also be disseminated to the university libraries found in the country if possible. Publication of the material on international medical journals is also a priority of the author. The findings of the research will also be discussed to the subjects of the study by staffs when the patient comes to the hospital for subsequent follow up.

6. Result

A total of 174 ALL patients admitted to hematology ward of TASH from January 01/ 2023 to July 31 /2024. This was 46.4% of the 375 of acute leukemia cases admitted to the institution during the study period.

6.1 Sociodemographic characteristics

From 174 cases admitted to hematology ward of TASH during the study period, 101 (58%) were males and 73 (42%) were females. The M:F ratio was 1.4.

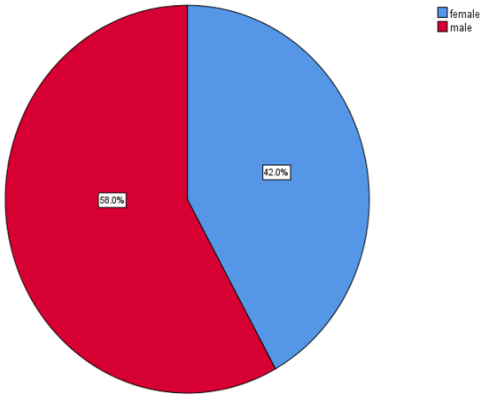


Figure 1: Sex distribution of ALL patients.

The mean age of the patients were 31.4 (SD ±14.743). The age range of patients was from 15 years to 78 years and the median was 28 years. The age group 20 to 29 years was the most commonly affected age group, 54 (31%) of patients. Followed by age group 14 to 19 years (44 cases – 25.3%) and 30 to 39 years (31 cases - 17.8%) of patients. There were 21 (12.1%) patients in age group of 40 to 49, 13 (7.5%) patients in age group of 50 to 59, 6 (3.4%) of patients in age group of 60 to 69 years and 5 (2.9%) patients in age group of 70 to 79 years. There was no patient above the age of 80 years.

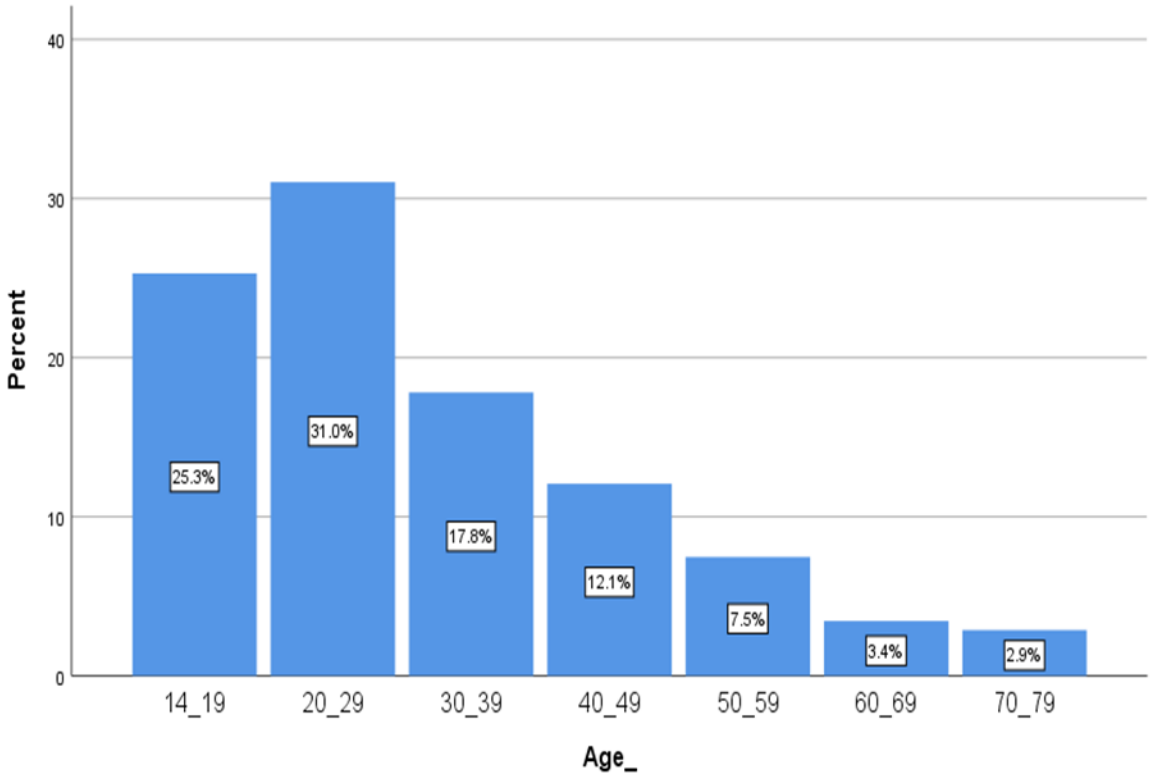


Figure 2: Age distribution of ALL patients

Most patients come from Oromia region (61 cases – 35.1%). 36 (20.7%) of patients come from the capital city, Addis Ababa. Amhara region were the residence for 31 (17.8%) of patients. 28 (16.1%) of patients come from South West Ethiopia region. 5 (2.9%) patients came from Sidama and Somalia region each. 3 (1.7%) people came from Tigray region. 2 (1.1%) patients come from Harari region. A single patient (0.6%) each, come from Benihangul Gumuz, Central Ethiopia region and Diredawa city.

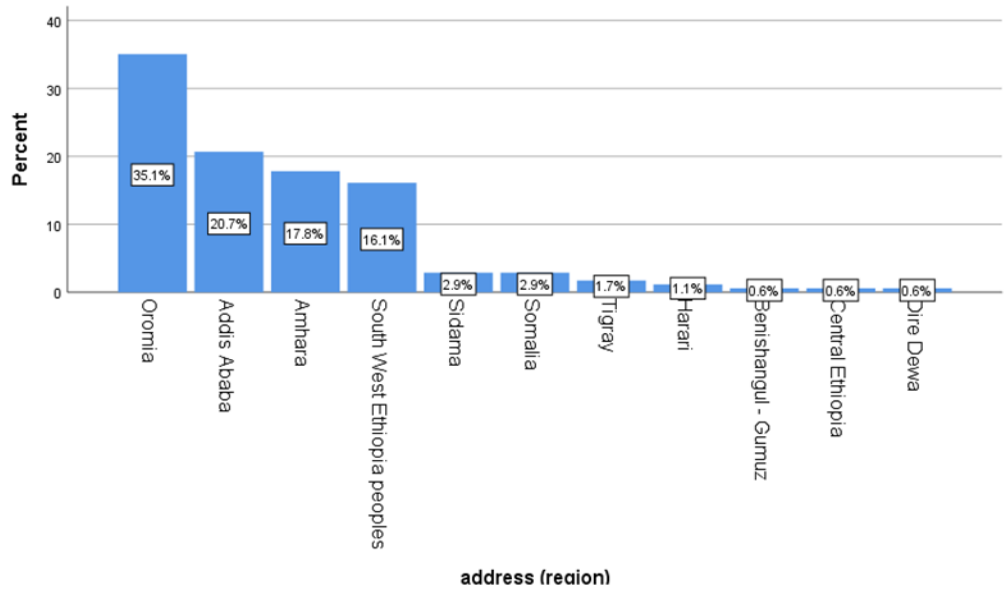


Figure 3: Address (region) of ALL patients

Patients from rural areas slightly higher in number than those patients who came from urban areas. 90 (51.7%) patients come from rural areas and 84 (48.3%) come from urban areas.

6.2 Disease Characteristics and Comorbidities

6.2.1 Clinical symptoms

The common symptom were symptoms of anemia, which were present in 160 (92%) of patients. The next common symptoms includes constitutional symptoms (122 – 70.1%), fever (93 – 53.4%) and bleeding tendencies (51 – 29.3%) of patients. Bone pain were present in 41 (23.6%) of patients. Abdominal swelling were reported in 37 (21.3%) of patients. Symptoms suggesting CNS involvement were present in only 6 (3.4%) of patients.

Table 1: Common symptoms in ALL patients

Symptoms	Yes	No
Symptoms of anemia	160 (92%)	14 (8%)
Constitutional symptoms	122 (70.1%)	52 (29.9%)
Fever	93 (53.4%)	81 (46.6%)
Bleeding tendencies	51 (29.3%)	123 (70.7%)
Bone pain	41 (23.6%)	133 (76.4%)
Abdominal swelling	37 (21.3%)	137 (78.7%)
Symptom of menigsmus	5 (2.9%)	169 (97.1%)
ABM	1 (0.5%)	173 (99.5%)

The duration of symptoms ranges from 1 week to 52 weeks. The mean duration of symptoms in weeks were 8.56 (SD ± 7.52). The median was 8 weeks. 20 (11.5%) patients reported symptom duration of less than 2weeks. 53 (30.5%) of patients have their symptom lasting 3 to 4 weeks. 50 patients (28.7%) have symptoms lasting 5 to 8 weeks. Only 3 (1.7%) of patients have symptoms longer than 6 months.

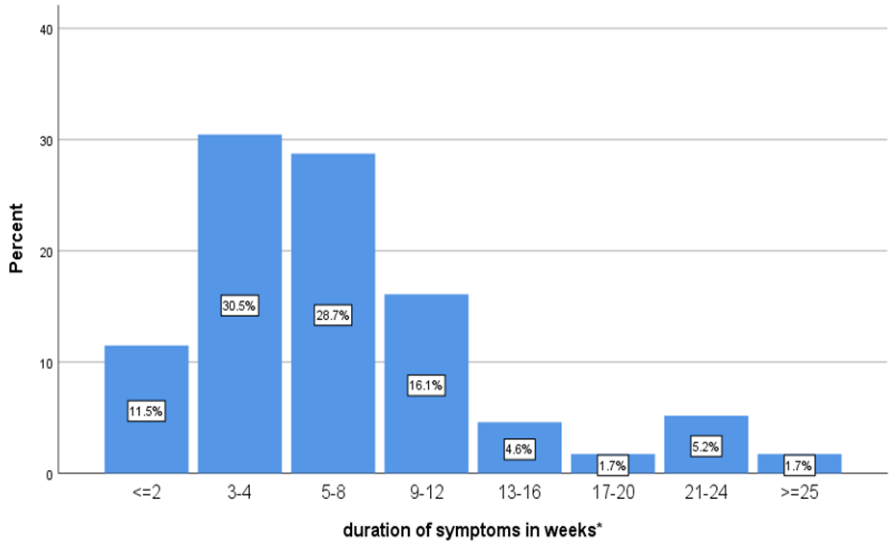


Figure 4: Duration of symptoms of ALL patients in weeks

6.2.2 Clinical signs

The most common sign were pallor, which were present in 152 (87.4%) of patients. Fever > 38^{o}C were present in 80 (46%) of patients. Lymphadenopathy were seen in 75 (43.1%) of patients and splenomegaly in 65 (37.4%) of patients. The median size of spleen in those patients who had splenomegaly was 6cm. The mean size of the spleen was 6.85 (± 3.25) cm. from those patients who had splenomegaly, 22 (32.8%) of patients had massive splenomegaly (>/= 8cm). Mucocutaneous bleeding were present in 35 (20.1%) of patients. 4 (2.3%) of patients had signs of menigismus.

Table 2: Common signs in ALL patients

Sign	Yes	No
Pallor	152 (87.4%)	22 (12.6%)
Fever > 38oC	80 (46%)	94 (54%)
Lymphadenopathy	75 (43.1%)	99 (56.9%)
Splenomegaly	65 (37.4%)	109 (62.6%)
Bone tenderness	57 (32.8%)	117 (67.2%)
Mucocutaneosu bleeding	35 (20.1%)	139 (79.9%)
Raised JVP	23 (13.2%)	151 (86.8%)
Meningeal signs	4 (2.3%)	170 (97.7%)

Regarding the performance status of patients at presentations, 95 (54.6%) of them had ECOG performance status of 0 or 1. 79 (45.4%) have ECOG performance status of >/= 2. Comorbidity was present in 35 (20.1%) of patients. 139 (79.9%) didn't have any comorbidity. The most commonly reported comorbidity was diabetes mellitus, which were present in 10 (5.7%) of patients. Hypertension was the second most common comorbidity seen in 9 (5.2%) of patients. Other comorbidities include pulmonary disorders in 2 (1.14%), heart failure in 6 (3.45%), RVI in 3 (1.7%) and CHBV in 4 (2.3%) of patients. Epilepsy, CLD and thyrotoxicosis were present in single patient each. One patient had three comorbidity at the same time.

6.2.3 Laboratory and pathologic results

When we see the CBC profile of ALL patients, the mean WBC count was 58,760 (SD ± 87, 059.24). The median was 17, 945 and the range was from 340 to 516,000/uL. 36 (20.7%) of patients have WBC count >100,000/uL. The mean hemoglobin level was 7.71g/dl (SD ± 3.025) the range was from 2g/dl to 16g/dl and the median was 7.55g/dl. 101 (58%) of patients have a hemoglobin level of </= 8 g/dl. The mean platelet count was 60, 736/ul (SD ± 82, 960). The range was from 2000/ul to 514,000/ul and the median was 28,000/ul. 33 (19%) of patients had a platelet count of < 10,000/ul. The mean LDH was 979.2 (SD ± 1107.89). The range was from 136 IU to 8306 IU and the median was 656IU. 74 (42.5%) of patients had LDH below the upper limit of normal. 100 (57.5%) of patients have LDH above the upper limit of the normal. The mean Uric acid level was 7.25 (SD ± 3.38)mg/dl. The range was from 1mg/dl to 21 mg/dl and the median was 6.5mg/dl. 20 (11.5%) percent of patients have tumor lysis syndrome. From these, 8 (4.6%) had clinical TLS. AKI was clinical TLS defining event in all of them.

Table 3: laboratory findings of ALL patients

Parameter	Mean	SD	Median	Range
WBC count /ul	58,760.8	± 87,059.24	17,945	340 – 516,000
Hemoglobin g/dl	7.71	±3.025	7.55	2 - 16
Platelet /ul	60,736	± 82,960	28,000	2000 – 516,000
LDH (IU)	979.2	± 1107.89	656	136 - 8306
Uric acid (mg/dl)	7.25	± 3.39	6.5	1 - 21
PB blasts (%)	53.51	± 28.98	60	0 - 97
BM blasts (%)	76.71	± 21.47	83	2 - 98

When we see the morphologic sub type of patients, 109 (62.6%) of patients had L2 morphology. L1 morphology was diagnosed in 52 (29.9%) of patients. There was no L3 morphology during the study period. In 7 (4%) of patients the FAB subtype were difficulty to determine. 6 (3.4%) of patients had lymphoblastic lymphoma.

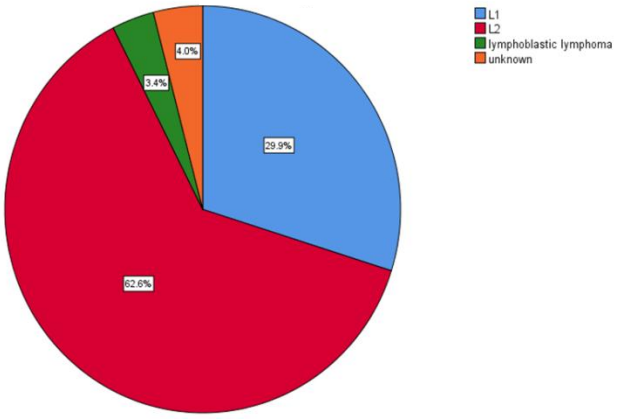
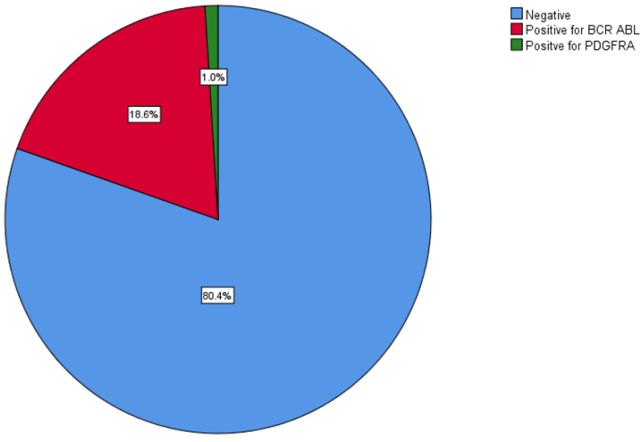


Figure 5: FAB morphologic sub type of ALL patients

The modalities used to reach the diagnosis includes morphology, IPT by flowcytometry and IHC and cytogenetic analysis. In 56 (32.2%) of patients, morphology was the only diagnostic modalities used. Morphology with IPT was used in 16 (9.2%) of patients. Morphology with cytogenetic analysis was done for 84 (48.3%) of patients. 18(10.3%) of patients have all 3 diagnostic modalities used for them to reach to their diagnosis. Over all 102 (58.6%) of patients had cytogenetic test done for them. The most commonly used genetic test was FISH. t(9,22) was done to all 102 cases. One patient, in addition to t(9,22), PDGFRA and PDGFRB rearrangement done for him. From this cytogenetics tests, 19 (18.6%) were positive for t(9,22). 83(81.4%) were negative. One patient had PDGFRA positive. The origin of the ALL in those patients who had IPT(34 patients), were 19 (55.9%) B cell and 15 (44.1%) were T cell.

Figure 6: Results of cytogenetic analysis for ALL



6.3 Treatment and Outcome

6.3.1 Treatment

Among 174 ALL patients admitted to hematology ward of TASH during the study period, 126 (72.4%) of them started on chemotherapy. From this, 112 (64.4%) started on induction therapy and 14 (8%) started on palliative therapy. 25 (14.4%) patients left hospital against medical advice before initiation. 20 (11.5%) died before initiation of chemotherapy. 3 (1.7%) of patients referred abroad.

The most commonly used induction regimen was CALGB 10403, which was used in 79 (70.5%) of patients who took induction therapy. CALGB 8811 was used in 13 (11.6%) of patients. Imatinib with vincristine and prednisolone was used for 18 (16.1%) of patients. One (0.9%) patients took Rituximab with CALGB 10403. One patient took imatinib only.

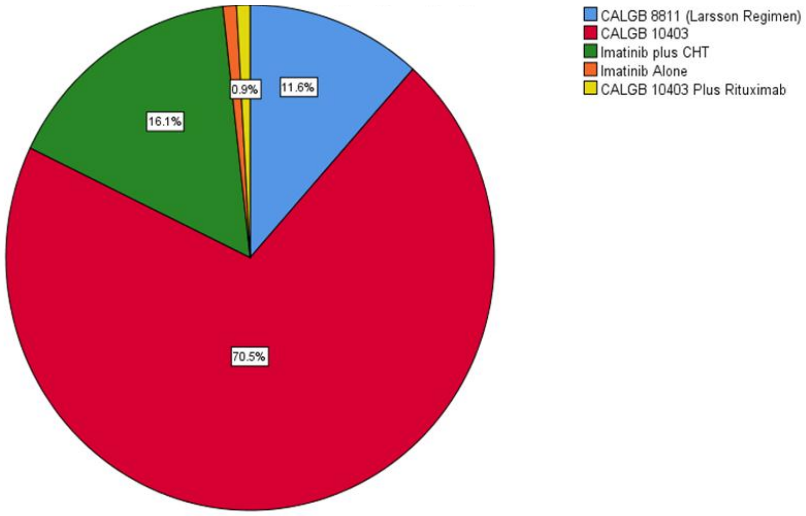


Figure 7: Type of regimens used for induction in ALL patients

The mean initiation of induction chemotherapy was 8.84 (SD ± 7.086) days from BM report day. The median was 7 days and the range was from 1 to 40 days. 58 (51.8%) of patients started induction treatment within 7 days of diagnosis. 31 (27.7%) was started within 8 14 days. 16 (14.3%) within 15 to 21 days. 5 (4.5%) took their induction between 21 and 28 days. 2(1.8%) of patients, induction chemotherapy was started after 28 days. When we see the initiation of induction therapy since ward admission, the mean was 8.88 (SD ± 7.258) days. The median was 6.5 days and the range was from 1 to 37 days. 60 (53.6%) of patients were started on induction therapy within 7 days of ward admission. 34 (30.4%) were started within 8 to 14 days. 12 (10.7%) were started between 15 to 21 days of ward admission. 2 (1.8%) patients started within 22 to 28 days. 4 (3.6%) of patients started on induction therapy after 28 days.

For 14 patients who started on palliative therapy, the combination of 6 MP, Vincristine, MTX and prednisolone (POMP regimen) was used in 9 (64.3%) of patients. Vincristine plus prednisolone was started in 5 (35.7%) of patients.

6.3.2 Treatment outcome

From 112 patients who took induction chemotherapy, 74 (66%) achieved CR. 33 (29.5%) patients died during induction. 3 (2.7%) of patients had refractory disease and 2 (1.8%) of patients defaulted before completion of induction chemotherapy.

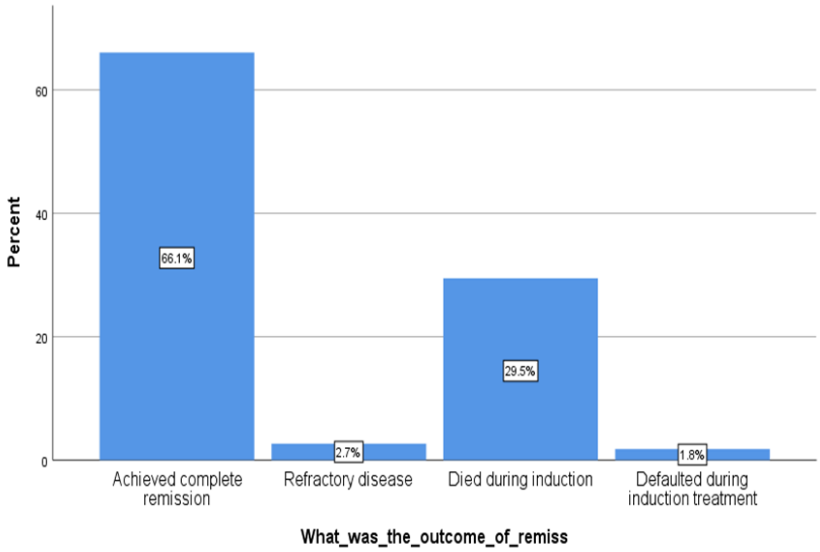


Figure 8: Outcome of induction CHT of ALL patients

Patients who took imatinib plus CHT have the highest CR rate 94.4%, followed by CALGB 10403, which had a CR rate of 63.3%. Male patients who took induction treatment have better CR rate than females. From 68 males who took induction treatment, 48 (70.6%) achieved CR. From 44 female patients who took induction treatment, 26 (59.1%) achieved CR. Ph positive ALL treated with imatinib plus CHT also had betted CR (90%) compared to Ph negative ALL (65.6%). There were 19 (31.1%) deaths in Ph negative ALL compared to 2 (10%) of deaths in Ph negative ALL. Patients between the age of 15 to 29 had a CR rate of 70.4% compared to that of 60.9% for age group of 30 to 39 years.

Table 4: Outcome of induction treatment with different regimen for ALL patients

Regimen	CR	Died	Refractory	Defaulted	Total
CALGB 8811	5 (38.5%)	6 (46.7%)	1 (7.7%)	1 (7.7%)	13
CALGB 10403	50 (63.3%)	26 (32.9%)	2 (2.5%)	1 (1.3%)	79
Imatinib + CHT	17 (94.4%)	1 (5.6%)	0	0	18
CALGB 10403 + Rituximab	1 (100%)	0	0	0	1
Imatinib alone	1 (100%)	0	0	0	1
Total	74 (66%)	33 (29.5%)	3 (2.7%)	2 (1.8%)	112

On bivariate analysis, urban residence, female sex, ECOG performance status ≥2, presence of comorbidities and presence of complications after induction CHT were all associated induction failure (outcome other than CR). But on multivariate analysis, only ECOG performance status ≥2 at presentation was associated with induction outcome.

Table 5: Results of bivariable and multivariable Cox regression analysis of induction outcome of ALL patients.

Variables	Category	COR (95% CI)	AOR (95% CI)	P Value
Residence	Urban	1	1	
	Rural	1.6 (0.74, 3.58)	0.24 (0.23, 2.42)	0.224
Sex	Female	1	1	
	Male	0.6 (0.27, 1.330	0.82 (0.69, 9.69)	0.874
LAP	No	1	1	
	Yes	2.26 (0.17,1.5)	6.46(0.49, 83.55)	0.153
ECOG	O and 1	1	1	
	≥ 2	3.25 (1.44, 7.34)	0.066 (0.007, 0.64)	0.019
Comorbidity	No	1	1	
	Yes	1.78 (0.66, 7.34)	0.34 (0.009, 12.39)	0.555
Complications	No	1	1	
	Yes	7.13 (1.57, 32.31)	0.17(0.000, 30.14)	0.503

Regarding to the final outcome of patients who took any kind of treatment at the data cut off date September 30/2024, 36 (28.6%) were alive. 66 (52.4%) are died and 24 (19%) patients are lost to follow up. There were 6 (5.3%) documented relapses during the study period. The time of relapses were while on delayed intensification treatment in 4 patients, one patient relapsed during interim maintenance phase of treatment and the last patient while on prolonged maintenance phase of treatment. When we see regimens used prior to relapse, 5 of the relapsed patients took CALGB 10403 (with or with out imatinib based on the Philadelphia chromosome status) and the other one took Larsson regimen as treatment regimen prior to relapse. 2 out of 6 relapses occurred in Ph positive ALL. Regarding to the sites of relapse, 2 of the relapses were in the BM. One patient had a relapse both in BM and CNS. The other three patients had relapses in the CNS alone. When we see the treatment and outcome of relapsed ALL patients, 2 patients died without treatment of relapse. One patient switched to dasatinib and given Cranial irradiation but died. One patient switched to dasatinib and POMP started. He is currently alive. One patient is currently alive on POMP. One patient died after TIT started for the CNS relapse.

Table 6: Final outcome of ALL patients

Final outcome	Number	Percent
Alive on the interim maintenance phase of treatment	1	0.8
Alive on delayed intensification phase of treatment	5	4
Alive on prolonged maintenance phase of treatment	24	19
Alive on palliative treatment	3	2.4
Alive with relapse/refractory disease	3	2.4
Died	66	52.4
Lost to follow-up	24	19
Total	126	100

Regarding to factors associated increased risk of death, bivariate analysis showed that female sex, age <40 years, presence of constitutional symptoms, splenomegaly, ECOG ≥ 2 and presence of complications following induction therapy were all associated with increased risk of death. But on multivariate analysis female sex and ECOG ≥2 were associated with increased risk of death.

Table 7. Results of the bivariable and multivariable Cox regression analysis for death in ALL patients

Variables	Category	COR (95% CI)	AOR (95% CI)	P value
Sex	Female	1	1	
	Male	0.38 (0.16,0.91)	0.29 (0.001, 0.54)	0.018
Age	</= 40 Years	1	1	
	>40 years	1.42 (1.06,1.9)	0.33 (0.12, 6.32)	0.461
Constitutional symptoms	No	1	1	
	Yes	1.5 (0.65,3.3)	3.24 (0.23, 44.6)	0.38
Splenomegaly	No	1	1	
	Yes	0.36 (0.16,0.8)	0.15 (0.02,1.12)	0.065
ECOG Performance status	1 and 0	1	1	
	≥ 2	3.01 (1.31,6.88)	40 (2.4, 669.5)	0.01
Complication following post induction Rx	No	1	1	
	Yes	3.819 (1.25,11.7)	75.6 (0.43, 13,24)	0.101

Overall survival was calculated using Log Rank test for those patients who took any kind of chemotherapy and their final outcome was known. The mean survival time was approximately 259.85 days, with a standard error of 27.30 months. The 95% confidence interval for the mean survival time ranges from 206.35 to 313.35 days. The median survival time was approximately 87.00 days, with a standard error of 47.81 days. The 95% confidence interval for the median survival time ranges from 0.00 to 180.70 months.

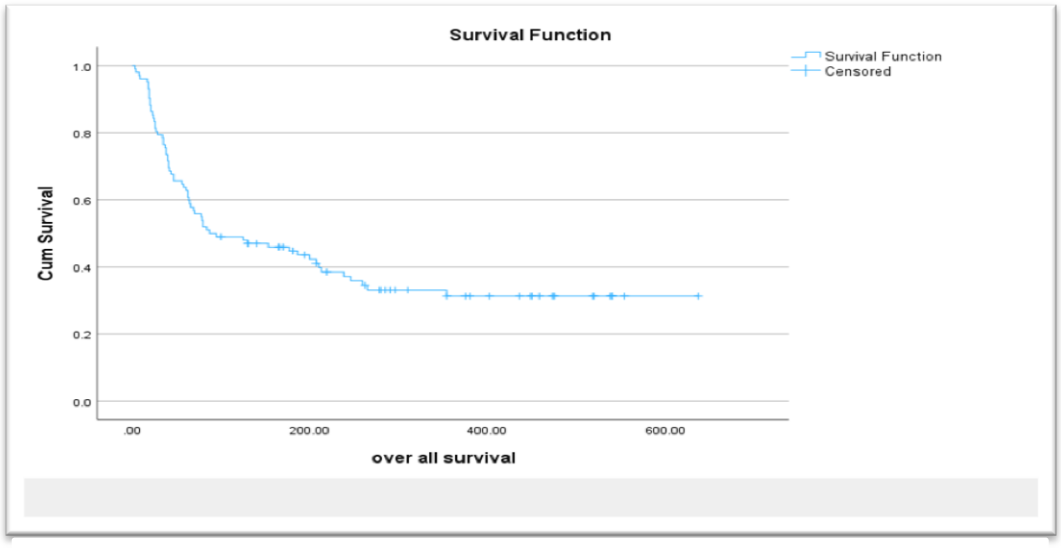


Figure 9: Kaplan Meier curve of ALL patients who took chemotherapy

6.3.3 Complications and causes of death

From 112 patients who was given induction chemotherapy, at least one kind of complication occurred in 89 (79.5%) of them. 23 (20.5%) didn't have any complication during induction chemotherapy. Few patients have multiple complications at the same time. The most common complication was neutropenic fever. It occurred in 81(91%) of patients who had complications.

Table 8: Common complications seen during induction CHT in ALL patients

Type of complications	Number	% from patients who have complication	% from all patients who took induction CHT
Neutropenic fever	81	91	72.3
Bleeding to vital organs	10	11.2	8.9
Thromboembolism	8	9	7.1
Hyperglycemia	5	5.6	4.4
DILI	21	23.6	18.75
Pancreatitis	2	2.2	1.8

The most common focus of infection was GI and Muccossa. 42 (51.9%) of patients have GI and mucosal focus of infection. Chest was the focus of infection in 36 (44.4%) of patients. Skin and soft tissue focus was identified in 7 (8.6%) of patients. CNS infections were seen in 6 (7.4%) of patients. The focus of infection was not identified in 8 (9.9%) of patients. One patient had mucormycosis. When we see microbiologic diagnosis, 79 (97.5%) out of 81 patients had blood culture. Blood culture was not sent for 2 (2.5%) of patients. 6 (7.6%) of patients have positive blood culture and 73 (92.4%) had negative blood culture. The most commonly isolated organism was Klebsiella pneumonea (in 3 patients). Pseudomonans aeroginosa, Enterococcus and CONS were cultured one time each.

Bleeding to vital organs was seen in 10 patients. ICH occurred in 6 patients. UGIB were present in 3 patients and DAH in single patient. Thromoembolism were seen in 8 patients. The most common site of thrombosis was cerebral vein. CVT were present in 4 patients. DVT was present in 3 patient and PTE in one patient. All patients were initially anticoagulated with UFH/Enoxaparin. Except one patient, all of them switched to rivaroxaban for long term anticoagulation.

There were a total of 86 documented deaths. 66 patients died after initiation of treatment (palliative or curative). 20 patients were died before initiation of chemotherapy. This didn't include patients who were lost to follow up and died without documentation. The most common cause of death was sepsis and septic shock. This was the cause of death in 72 (83.7%) of patients. Progressive disease was the cause of death in 13 (15.1%) of patients. Multiple causes of death were mentioned for few patients.

Table 9: Common causes of death in ALL patients

Cause of death	Number	Percent
Sepsis and septic shock	72	83.7%
Progressive disease	13	15.1%
Bleeding to vital organs	6	6.9%
Liver failure	2	2.3%
Thromboembolism	3	3.5%
Summary of death insufficient	5	5.8%
Others (ADHF, Peritonitis 2o? MT…)	6	6.9%

7. Discussion

Adult ALL is a common referral diagnosis to TASH. From 375 acute leukemia patients admitted to hematology ward of TASH during the study period, 174 (46.4%) were ALL. This figure is comparable to previous studies done in this hospital. A 5 years retrospective study done on 2019 by Lallise et. al which included 235 patients, reported 94 (40%) were being ALL (5). Another study in the same institution by Shamebo, the proportion of ALL was 46.3% (8).

The M: F ratio in this study was 1.4. Most literatures reported male predominance in ALL. A study in Algeria reported a M:F ratio of 1.9, even though this study included both types of acute leukemia (14). Another study in Morocco specifically on ALL patients reported M:F ratio of 1.05 (16). Another study in Southern China by Su Yi Li reported a M:F of 1.8 (17). The above mentioned study by Lalliseet.al, reported M:F of 1.58 for both types of acute leukemia (5). All six lymphoblastic lymphoma cases in our study were males.

The mean age of all ALL patients in our study was 31.4. (SD ± 13.743) and median was 28 years. The age distribution was different for male and female patients. The mean age for female patients were 35.04 year (SD ± 1.778) and the median was 32. The mean age for male patients were 28.76 (SD ± 1.383) and the median was 25. This difference in age the two genders was also reported by the study done by Su Yi Li in southern China (17). The age of Ph positive patients in this study was also comparable with the other patients. The mean for this group of patients was 33.65 (SD ±15.3080 years, range was 15 years to 72 years and the median was 29.5 years.

The most common clinical manifestation of ALL patients in this study was anemia. This was present in 92% of patients. This symptom was also the commonest in other studies (5, 8, 14, 18). Lymphadenopathy and splenomegaly were seen in 43.1% and 37.4% of patients respectively. This was lower proportion than a study done in India on 530 patients where hepatosplenomegaly present in 80% and lymphadenopathy 79% of patients (19). The rate of TLS in this study was 11.5%. Clinical TLS was seen only in 4.6% of patients. This is relatively low compared other studies. In review of 398 children diagnosed with ALL conducted by Al Bagshi, the TLS incidence was 19% (20). Another study by Bahoush et al. conducted on 160 children with ALL reported a 26% incidence of TLS (21). Despite adequate work up for TLS at presentation, the reason for low incidence of TLS in our patients requires further study.

L2 morphology was the most common subtype which occurred in 62.6% of patients. L1 morphology was seen in 29.9% of patients. There was no L3 morphology during the study period. The study by Lallise et al. also reported the similar findings. In that study, L2 morphology was accounted for 52.1%, l1 morphology 7.4% and L3 morphology 3.2% (5). 6 lymphoblastic lymphoma patients were present in this study. As expected, their diagnosis is settled by IPT from lymph node. Consistent with most literatures, all lymphoblastic lymphoma patients were males (16).

Treatment outcome for induction chemotherapy in this study was 66%. There was variation in CR rate based on the type of regimen used. In patients where CALGB 10403 was used, the CR rate was 63.3% and induction mortality was 32.9%.In the original trial where 295 patients included in the final analysis, the median age was 24 and the CR rate was 89% with only 3 induction deaths (11). The difference is expected due to the better health care system in US. In a study done in Malawi, only 15 patients were included and the median age was 22, from those patients who started CALGB 10403 protocol, CR rate was 73%, 1(7%) patient died and 2 (13%) had a refractory disease (33). Despite the fact Malawi is a developing country, the CR was better. But due to small number of patients it is difficult to make conclusion.

When we see the result of the original CALGB 8811 trial, 197 patients were included in the final analysis. The median age was 32 years. 85% of patients achieved CR and 9% of patients died (12). When we look at 13 patients in our study for whom this protocol was used, CR rate was38.5% and induction mortality was 46.7%. This huge gap is the reflection of the health care provided by the two countries. Overall, the outcome of ALL in our center is characterized by early deaths, relatively lower CR rate and high induction mortality. There was also significant number of lost to follow up cases.

This high mortality rate associated with ALL in our setup compared to other studies was due to infection. Sepsis and septic shock was responsible for 83.7% of deaths. Poor ward conditions, absence of adequate antibacterial and antifungal agents were the huge factor for this infection related mortalities. It is imperative to be ready such kind of infection before giving this highly toxic chemotherapy regimens for the patients.

8. Conclusion

ALL is one of the commonest referral diagnoses to TASH. 174 cases in 19 months of study period is a high number. Despite the large number of cases, there is gap in terms of diagnosis and treatment. Diagnosis is mostly morphology based which is not the standard currently recommended by WHO/ICC. Immunopheotyping by flowcytomentry and IHC are currently not available in the hospital. The management of ALL was characterized by early deaths and self-discharge. In those patients who started treatment, lower CR rate and high induction mortality were the features. Frequent interruption and lost to follow up were also the main problems. Infection related deaths were very common, reflecting very poor infection control in such patients.

9. Recommendations

Based on the study findings the following recommendations are forwarded.

For ALL patients and the community:

- Despite the fact that ALL is a killer disease, it is also treatable and have good prognosis in certain group of patients.
- To seek health care early before the disease complicated by infections, bleeding as the treatment outcome will be worse once these complications appeared.
- To pursue the health care and avoid interruption as complications appeared rapidly once medical follow up discontinued.
- To participate in donation of blood as this blood products are very important for management of this patients

For physicians:-

- Since ALL requires urgent diagnosis and treatment, it is better to refer patients for hematologist evaluation early once the diagnosis is suspected
- Once patients are diagnosed with ALL, they require close follow up to see for disease and treatment related complications.
- To change the attitude that ALL is a killer disease whether treated or not. Advances in diagnosis and therapy currently makes ALL treatment to have a good outcome.

To policy makers:-

- To facilitate the availability of diagnostic modality which are the corner stone for reaching the diagnosis and selection of treatment.
- To make essential drugs such as chemotherapy, GCSF, antibiotics and antifungals readily available
- To establish HSCT center because currently treatment of ALL without this modality of management is not recommended.
- Need to adjust the type of chemotherapy regimens given for ALL patients in our setup as this was related to high mortality rate in this study.

For researchers:-

- To study the true incidence of ALL and its burden as this makes it easier for decision making.

10. Strength and limitation of the study

10.1 Strength of the Study

The study was done at TASH, one of the oldest and well recognized hospital. It is also the only center in the country which is equipped for treatment of ALL. This enables the study to have adequate number of patients, 174, to see the burden of the problem. Being prospective study also increased the quality of data that were collected and avoids missing of cases. Unlike previous studies done on acute leukemia, it only includes patients with ALL and this helped to identify the true demographic, clinical and treatment aspects of the disease. As far as our knowledge, this is the only prospective study in Africa involving large number of patients with this specific type of acute leukemia only.

10.2 Limitation of the study

The short follow up period, that is 21 months, makes it difficult to assess the long term outcome of the few surviving patients. In addition to that large number of patients who were documented as lost to follow up reduced the power of the study to identify factors which were related to important outcome variables.

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12. Annexes

Annex I: Data Collection tool for the Study of Acute Lymphoblastic Leukemia at TASH

Acute Lymphoid Leukemia (ALL)

Serial No: _____ Chart Number (MRN):_____
Phone No _____

A. Demographic data:

Name (Initial): _____ Address (Region): _____
Age: _____
Area of residence: Urban_____ Rural_____ Unknown_____
Sex: _____ Date of Admission-: _____
Date of admission to hematology ward
Date of ALL diagnosis (BM report date): _____

B. Presenting symptoms:

B1. Fever 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. Constitutional symptoms: 1. Yes 2. No 3. Unknown
B5. Bone pain: 1. Yes 2. No 3. Unknown
B6. Symptoms of meningismus: 1. Yes 2. No 3. Unknown
B7. Other, specify: _____

C. Duration of symptoms (in weeks):_____

D. Presenting signs:

D1. Fever > 380C: 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. Performance status
D10. Other, specify: _____

E. Did the patient have comorbid condition?

1. No
2. Yes

If yes, specify: _____

Workup:

F. laboratory findings at presentation:
F1. WBC (/uL):_____
F2. HGB (g/dL):_____
F3. Platelet count (/uL):_____
F4. Peripheral blast count (%) _____
F5. Bone marrow blast count (%) _____
F6. LDH (IU):_____
F7. Uric Acid (mg/dL):_____
F8. Creatinine (mg/dL):_____
F9. K:_____ PO4: _____ Ca: _____
F9. Tumor lysis syndrome (according to Cairo Bishop Criteria**) 1. Yes 2. No 3. Unknown
F10. CSF Analysis at day 8 Cell count---------- Cytology----------

Other:_____

G. Which modality was used for the diagnosis of ALL?

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

H. What was the subtype according to FAB classification (L1, L2, L3, unknown)?
Specify _____

I. If flowcytometry was done, what was the type according to WHO classification? Specify _____ (pre-B ALL, pre T-ALL, mature B-ALL, unknown)

J. If cytogenetics (BCR-ABL) test was done, what was the result? POS:_____ Neg:_____ Unknown:_____

Treatment and outcome:

K. Status of chemotherapy treatment?

A. Died before initiation of chemotherapy

B. Induction treatment initiated

C. Palliative treatment, specify _____

L. If induction chemotherapy was initiated, how many days after:

L1. Diagnosis (BM report day)? _____

L2. Ward admission? _____

M. Which regimen was used for remission-induction treatment?

1. CALGB 8811 (Larson Regimen)
2. Pediatric-inspired regimen - CALGB 10403
3. Imatinib plus chemotherapy
4. Palliative treatment, specify: _____
5. Other regimen, specify: _____

N. Were there any complication noted during remission-induction treatment (multiple answers possible) with the grade of AEs, if possible?

1. Neutropenic fever

1.1 Focus of NF if identified

2. Bleeding to vital organs, specify _____

3. Severe electrolyte derangement, specify _____

4. Coagulation abnormality, specify _____

5. Pancreatitis

6. Hepatic, specify _____

7. Neurologic, specify _____

8. Anaphylaxis, specify _____

9. Hyperglycemia

10. Other, specify _____

O. If the patient had infection during his/her stay, was blood culture taken?

1. Yes

2. No

P. If yes, what was the result (if culture was taken multiple times, specify all results)?

1. Positive Growth (specify isolated organism)_____

2. No Growth

3. Unknown

Q. What was the outcome of remission-induction therapy?

1. Died during induction

2. Defaulted during induction treatment

3. Achieved complete remission

4. Refractory disease

R. If the patient was given treatment, what was the final outcome/Phase of chemotherapy during data collection?

1. Alive on early intensification phase of treatment with maintained complete remission

2. Alive on the interim maintenance phase of treatment

3. Alive on delayed intensification phase of treatment

4. Alive on prolonged maintenance phase of treatment

5. Alive after completion of treatment with maintained complete remission

6. Alive on palliative treatment with complete remission

7. Alive with relapse/refractory disease

8. Died

9. Lost to follow-up

10. Other, specify:_____

S. If the patient is currently alive, what is the duration of outcome measures (in months) from the diagnosis (BM report day)? _____

T. If the patient has died, what is the duration of outcome measure (in months) from the diagnosis (BM report day)? _____

U. If the patient has died, what was the presumed cause of death?

1. Progression of disease
2. Liver failure
3. Thrombo-embolism
4. Ventricular tachycardia
5. Renal failure
6. Sepsis
7. Other, specify_____
8. Summary of deaths Unknown (Insufficient Information)

V. If the patient developed relapse, when did he/she relapsed?

1. During consolidation/interim maintenance/late intensification phase of treatment
2. During late maintenance phase of treatment
3. Within 6months of completion of maintenance treatment
4. After 6months of completion of maintenance treatment

W. If the patient developed relapse, where was the site of relapse? Specify

X. What regimen did she/he take after relapse?

1. Re-induction with similar regimen(Specify)_____
2. Re-induction with different regimen (Specify)_____
3. Palliative care(Specify)_____
4. Underwent allogenic SCT at different set up
5. Unknown
6. Other, specify_____

Y. What was the response for re-treatment after relapse?

1. Died during treatment
2. Defaulted during treatment
3. Achieved second complete remission, (Specify duration of CR)_____
4. Refractory disease

Annex II: Cairo-Bishop definition for TLS

Laboratory TLS: abnormality in >2 of the following, occurring within 3days before or 7days after chemo

- uric acid > 8 mg/dL or 25% increase
- potassium > 6 meq/L or 25% increase
- phosphate > 4.5 mg/dL or 25% increase
- calcium < 7 mg/dL or 25% decrease

Clinical TLS: laboratory tumor lysis syndrome plus one or more of the following:

- Increased serum creatinine (1.5 times upper limit of normal)
- Cardiac arrhythmia or sudden death
- Seizure

Annex III: ECOG Performance status

0 – Fully active, No performance restrictions

1- Strenuous physical activity not restricted, Fully ambulatory and able to carry out light work

2- Capable of self-care but unable to carry out any work activities. Up and about >50% of waking hours

3- Capable of only limited self-care, confined to bed or chair>50% of waking hours

4- Completely disabled, cannot carry out any self-care. Totally confined to bed or chair

Annex IV: Types of leukemia

	Acute	Chronic
Myeloid origin	Acute myeloid leukemia(AML)	Chronic Myeloid Leukemia(CML)
Lymphoid origin	Acute Lymphoid Leukemia (ALL)	Chronic Lymphoid Leukemia(CLL)

Annex V: Classification of ALL

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
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor (ETP) lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Annex VI: Classification of B cell ALL

ALL cells	EGIL	TdT	CD19/22/79a	CD10	CyIg	Sig
Pro B ALL	Type I	+	+	-	-	-
Common ALL	Type II	+	+	+	-	-
Pre B ALL	Type III	+	+	+	+	-
Mature B ALL	Type IV	-	+	+/-	+	+

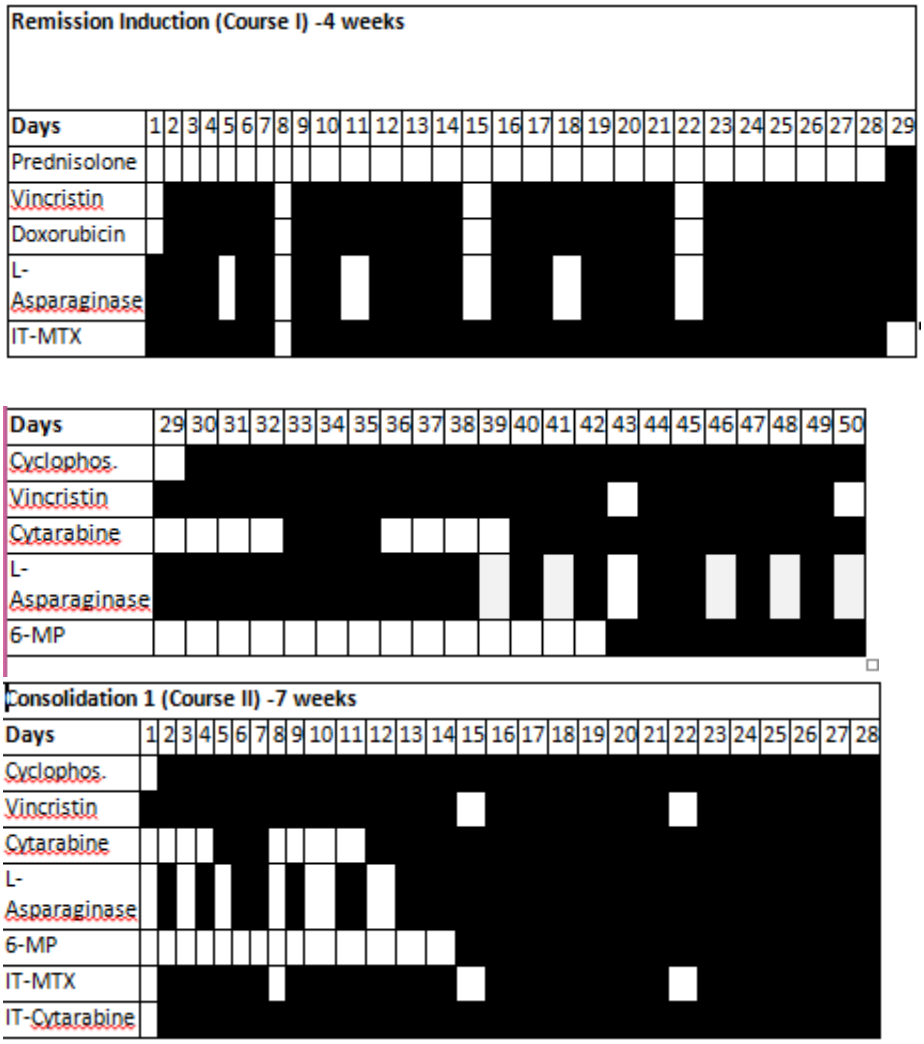
Annex VII: Classification of T cell ALL

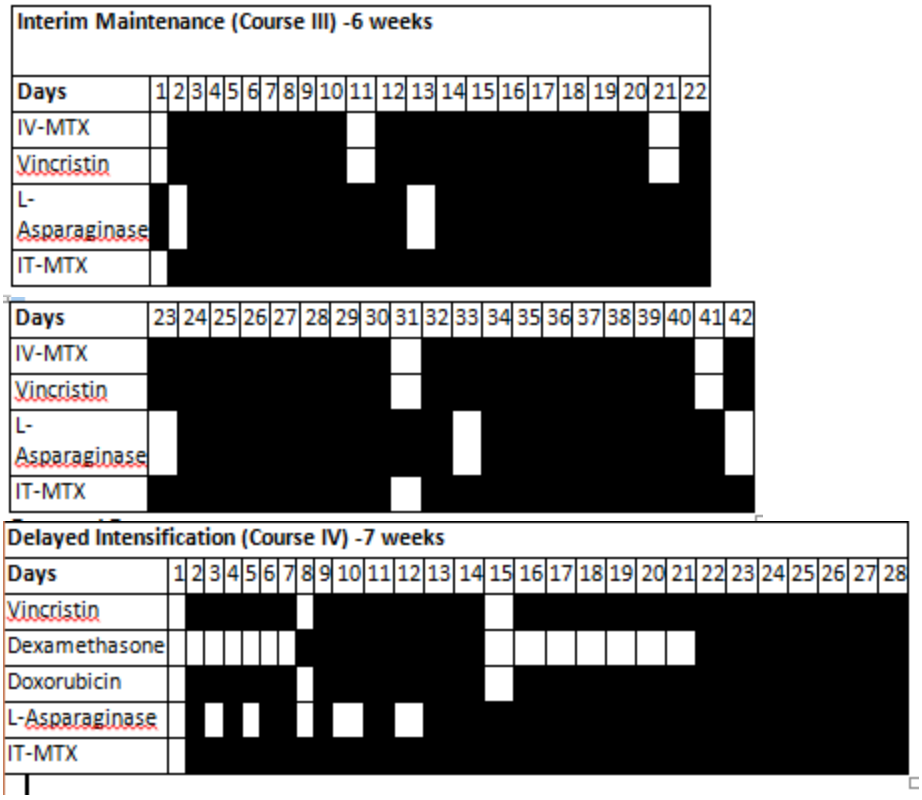
Marker	Pro-T-ALL (EGIL T-I)	Immature thymocyte (EGIL T-II)	Cortical T-ALL (EGIL T-III)	Mature T-ALL (EGIL T-IV)
TdT	++	++	++	++
CD1a	-	-	++	-
CD2	+	++	++	++
CyCD3	++	++	++	++
CD5	-	++	++	++
CD7	++	++	++	++
mCD3	-	-	+/-	++
CD4-/CD8-	-	++	-	-

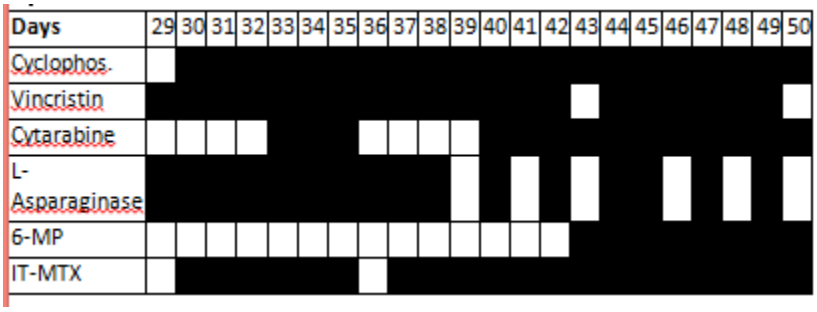
Table VIII: FAB classification of ALL

Type	Prevalence	Age distribution	Morphology
L1	30%	Adult type	Small, high N:C ratio, indistinct nucleoli, open chromatin & no CPGs
L2	65%	Childhood	Intermediate to large, heterogenous. One or two prominent nucleoli
L3	5%	Burkitt	Large, homogenous cells with prominent nucleoli. Intensely basophilic cytoplasm with vacuoles.

Annex IX: Pediatric Inspired ALL Protocol -CALGB 10403 (for 15-39 years of age)

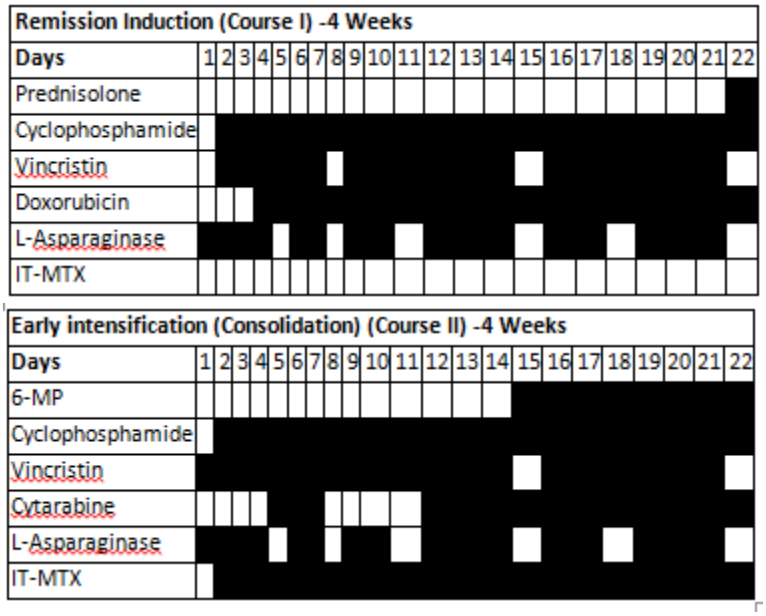






Maintenance (Course V) -12 weeks		
Drug	**Dose and Route**	**Schedule**
Vincristin	1.5 mg/m2 (max. 2mg) IV	On day every month
Prednisolone	100mg	On day 1 to 5 every month
6-MP	75 mg/m2/day PO	On day 1-84
Methotrexate	20 mg/m2 PO	weekly till day 78 (held on day 29 of the first 4 courses when IT-MTX is given)
IT-MTX	15 mg IT	On day 1 and 29

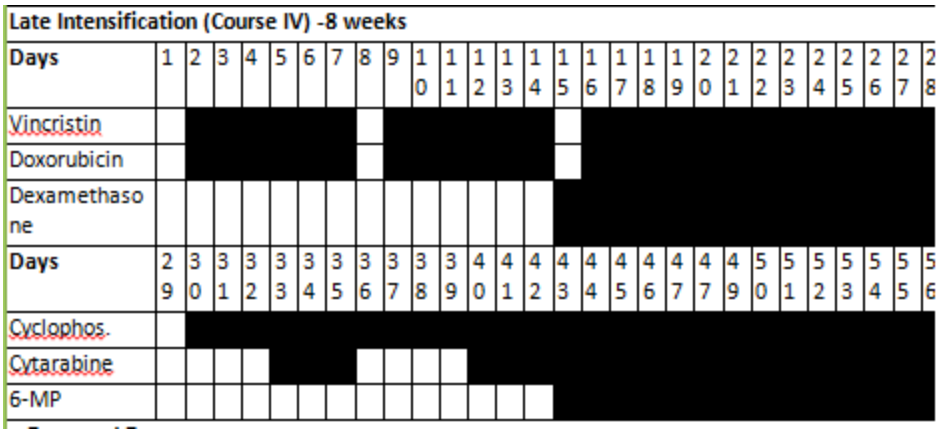
Annex X: Adult ALL Protocol CALGB 8811 (Age ≥40 years)



Remission Induction (Course I) -4 Weeks																						
Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Prednisolone																						■
Cyclophosphamide		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Vincristin		■	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■	■	
Doxorubicin				■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
L-Asparaginase	■	■	■	■		■		■		■		■	■	■		■	■		■	■	■	
IT-MTX																						

Early intensification (Consolidation) (Course II) -4 Weeks																						
Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
6-MP															■	■	■	■	■	■	■	■
Cyclophosphamide		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Vincristin	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	
Cytarabine					■										■	■	■	■	■	■	■	■
L-Asparaginase	■	■	■	■		■		■		■	■					■		■				
IT-MTX		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

CNS Prophylaxis and Interim Maintenance (Course III) -12 Weeks																						
Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
6-MP																						
IT-MTX		■	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■	■	
Days	23	24	25	26	27	28	29	30	31	31	33	34	35	36	37	38	39	40	41	42	43	44
6-MP																						
PO-MTX	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■		■
IT-MTX	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Days	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66
6-MP																						
PO-MTX	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■	■		■	■
Days	67	68	69	70																		
6-MP																						



Maintenance (Course V) -12 weeks		
Drug	**Dose and Route**	**Schedule**
Vincristin	1.5 mg/m2 (max. 2mg) IV	On day every month
Prednisolone	100mg	On day 1 to 5 every month
6-MP	75 mg/m2/day PO	On day 1-84
Methotrexate	20 mg/m2 PO	weekly till day 78 (held on day 29 of the first 4 courses when IT-MTX is given)
IT-MTX	15 mg IT	On day 1 and 29