EARLY TREATMENT-RELATED MORBIDITY AND MORTALITY OF CHILDREN WITH NON-HODGKIN'S LYMPHOMA TREATED AT TIKR ANBESA SPECIALIZED HOSPITAL WITH MODIFIED ALCL PROTOCOL: PROSPECTIVE COHORT STUDY

Addis Ababa University

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A Research Paper to be submitted to the Pediatric Hematology and Oncology Unit, Department of Pediatrics and Child Health, School of Medicine, College of Health Sciences, Addis Ababa University in Partial Fulfillment of the Requirements for the Sub-Specialty Certificate in Pediatrics Hematology and Oncology

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September 2024, Addis Ababa, Ethiopia

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A RESEARCH THESIS TO BE SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES; PEDIATRICS AND CHILD HEALTH DEPARTMENT IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE SUB-SPECIALTY CERTIFICATE PROGRAM IN PEDIATRICS HEMATOLOGY-ONCOLOGY

SEPTEMBER, 2024 .

ADDIS ABABA UNIVERSITY, COLLAGE OF HEALTH SCIENCE, DEPARTMENT OF PEDIATRICS AND CHILD HEALTH, PEDIATRICS HEMATOLOGY ONCOLOGY UNIT

I, the undersigned pediatrics hematology-oncology fellow Declare that I have submitted my original thesis on Early treatment-related mortality and morbidity of children with non-Hodgkin lymphoma treated at Tikur Anbessa specialized hospital with modified ALCL protocol; Addis Ababa Ethiopia in partial fulfillment of pediatrics hematology oncology sub-specialty program

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September, 2024

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Acronyms

NHL	Non-Hodgkin's Lymphoma
HL	Hodgkin's Lymphoma
BL	Burkitt Lymphoma
DLBCL	Diffuse Large B Cell Lymphoma
ALCLL	Anaplastic Large Cell Lymphoma
LL	Lymphoblastic Lymphoma
ALL	Acute Lymphoblastic Leukemia
HIC	High Income Country
LMIC	Low- and Middle-Income Countries
ICU	Intensive Care Unit
ROPD	Regular Outpatient Department
BFM	Berlin-Frankfurt - Munich
NCI	National Cancer Institute
TASH	Tikur Anbesa Specialized Hospital

Acknowledgment

I want to express my deepest gratitude to Addis Ababa University College of Health Sciences, Department of Pediatrics and Child Health for allocating the budget and giving me the chance. I would also like to thank the ASLAN Project for their invaluable support for my research. Lastly, I want to express my heartful gratitude to my advisors Dr. Haileyesus Adam and Professor Sheila Weitzman for their invaluable comments and support throughout the development of the proposal and their interest and readiness to help me until the end of the study.

Abstract

Background: - Childhood non-Hodgkin lymphoma is a varied collection of malignant neoplasms that includes all lymphomas that are not categorized as Hodgkin lymphoma. It is the third most prevalent malignancy after leukemia and brain tumors. Over the last twenty years, significant improvements in chemotherapy combination, intensification, and supportive care have led to significant survival in high-income countries. However, in low- and middle-income countries, underlying malnutrition, delayed and advanced presentation, inadequate supportive care, and infection will all lead to poor overall outcomes and treatment-related early or late mortality; this study aimed to Assess, early induction phase treatment-related mortality and associated factors of children with non-Hodgkin's Lymphoma treated at TASH treated with modified ALCL protocol.

Methods: - A hospital-based Prospective cohort study design was conducted on a total of 50 children with confirmed non-Hodgkin's lymphoma treated at Tikur Anbesa specialized hospital from March 2023 to June 2024. data were collected using a structured questionnaire and entered into Epi Data 3.1 then exported to SPSS for analysis. The categorical variables in the study were presented using frequency, and percentage, and compared between groups using the chi-square test. Multivariate logistic regression analysis, cox proportional hazard ratio, and Kaplan Meier analysis were performed to analyze the survival and factors associated with early treatment-related mortality.

Results: the mean age at diagnosis was 5 years; abdominal swelling and constitutional symptoms like fever and weight loss were the common presenting complaints. Burkitt lymphoma accounts for 40% of the diagnosis and the majority of the patients present with advanced stage of the disease with elevated LDH (86%), and stage III/IV disease (92%). The majority of the patients had one or more oncologic emergencies at presentation the commonest being TLS (56%) and infection (32%). Infectious complications, hematologic toxicity, mucositis, and typhlitis were the commonly encountered chemotherapy-related toxicities and 24% of patients died during the induction phase.

Conclusion: The induction phase of treatment resulted in a significantly high death rate (24%) for children and adolescents with NHL who were treated by the locally modified ALCL protocol.

Chapter 1: Introduction

1.1 Background

Lymphomas are neoplastic disorders caused by malignant transformation of the constituent cells of the lymphoid organs. Lymphoma broadly classified as Hodgkins and non-Hodgkins; accounts for 15% of childhood malignancies and they are the third most common after leukemia and brain tumor (1,2).

Childhood non-Hodgkin lymphoma (NHL) is a broad category of malignant neoplasms comprising all malignant lymphomas not otherwise categorized as Hodgkin lymphoma (HL). They constitute 60% of the lymphoma below the age group of 20 years, the commonest being Burkitt lymphoma (40%). However, in some areas, the prevalence of some NHL subtypes is significantly higher. similar to endemic Burkitt lymphoma, which constitutes 74% of all pediatric cancer cases in equatorial Africa. (1–4).

The majority of children with NHL, in contrast to adults, typically exhibit an aggressive disseminated disease. Roughly 70% of kids have advanced disease that involves the gastrointestinal tract, additional nodes, and widespread nodes. Particularly bone marrow, and central nervous system (CNS) Involvement affects the treatment and outcomes of all subtypes of childhood NHL. Most of the affected children also present with any one or a combination of these life or organ-threatening oncologic emergencies including TLS, superior/inferior vena cava obstruction, acute airway obstruction, spinal cord compression, pericardial tamponade, intussusception/intestinal obstruction, central nervous system (CNS) complications[2,6,7].

Major advances have been made in the diagnostic work-up, proper staging, and risk stratifications of the different subtypes of pediatric and adolescent NHL. Currently, the risk stratification is based on the St. Jude staging and grouping system. From the different patient and disease-related characteristics older age, elevated LDH, higher stage disease with involvement of the mediastinum, CNS, and marrow are poor prognostic indicators[10–13]. Additionally, in resource-limited settings low hemoglobin concentration. and HIV infection has been found to impact both the incidence and survival rates of patients with NHL(10).

Currently, the primary modalities of treatment of NHL include multi-agent systemic chemotherapy, immunotherapy, and occasionally definitive surgery with all the supportive

treatment. The selection of chemotherapy demonstrates a progressive progression, starting with a single cytotoxic agent such as prednisolone and cyclophosphamide, which improves survival in children with Burkitt lymphoma, and continue with combination chemotherapy for acute leukemia, which is still effective today, particularly in children with NHL that is in the early stages. With the refinement of chemotherapy and the supportive treatment the five-year event-free survival rates improved to 85 to 95% for early-stage disease and 70% to 90% for advanced-stage disease. CNS-directed therapy was recognized as an important component of these successful regimens, especially for children with LBL and BL. For both early- and advanced-stage NHL, the addition of RT to chemotherapy has not been demonstrated to increase survival. Debulking procedures have no place in the care of children with NHL.(7,11–14).

The reduction in early mortality due to TLS is another significant improvement. TLS and uric acid nephropathy are major risks for children with NHL, especially BL and LBL. With vigorous intravenous hydration, alkalization with sodium bicarbonate when allopurinol is administered, and careful monitoring of serum electrolytes, renal function test early death due to tumor lysis syndrome has been significantly decreased. In addition, cytoreduction prophase has been added to many regimens, which also helps achieve tumor control without increasing the risk of clinical deterioration during initiation of therapy. (15–17).

During the last thirty-five years, the prognosis for children and teenage NHL has significantly improved. Frontline therapy is used to cure almost 90% of children with mature B-cell lymphomas in high-income nations. In low- and middle-income countries (LMIC), cure rates range from 20% to 70% because of lack of diagnosis, misdiagnosis, abandonment of treatment, toxic death, and excess relapse with reduced-intensity regimens. Early toxic death associated with treatment or as a result of the disease is significant in low- and middle-income countries (LMIC) due to delayed presentation of severe disease and inadequate supportive care. The commonest causes of early death include infection, TLS, and bleeding(15,18,19).

1.2 Statement of The Problem

NHL is the third most common pediatric cancer in both LMIC and HICs following acute leukemia and brain tumor. Compared to HICs, LMICs have a greater rate of early mortality from NHL treatment. In HICs, the high standard of supportive care to handle early disease-related and treatment-related complications, the progressively improving trial-based treatment and increased awareness significantly reduced the morbidity and toxic death. In addition, the rate of complete remission and overall survival has been improved.

The challenges in LMICs like us include a lack of awareness that cancer is curable, late presentation, comorbid conditions like HIV, malnutrition, late diagnosis, improper staging, and risk stratification, poor supportive care, availability of ICU care, human resources and unavailability of chemotherapy and other supportive drugs. All this factor significantly increases morbidity and mortality, especially during the early treatment period. Because NHL treatment for children and adolescents is intense and administered periodically, it necessitates a large number of highly qualified staff, a well-designed treatment facility, an ongoing supply of antimicrobials and standard chemotherapy drugs, a steady supply of blood products, effective infection prevention programs, and strong psychosocial support.

Being one of the few oncology centers in the nation, Tikur Anbessa Specialized Hospital sees a large influx of cancer patients from all over the country. This has caused significant challenges including the treatment of NHL. The cornerstones of the care of children with NHL include prompt decision-making, handling of the oncologic emergency, early and quick workup to arrive at a diagnosis, and the beginning of definitive treatment with comprehensive supportive care. Giving prompt judgments is typically impossible due to a lack of human resources, particularly pediatric oncologists, as well as the necessary investigative methodology and supporting care. This impairs the therapy and, ultimately, the result for children with NHL.

Delays in diagnosis and treatment can have detrimental effects of their own, including increased risk of infection, needless hospitalization, and patient and parent discontent that can result in treatment abandonment and financial weariness. most of the patients are dying due to infection and bleeding and the Shortage of appropriate antimicrobials and blood and blood products which

we encounter in our daily practice are also expected to contribute to the low survival of children with NHL.

Critical care is one of the main components of increased survival. Patients with NHL typically need to be admitted to the intensive care unit (ICU) for treatment-related problems or malignancy. The low number of beds allocated for all children in the pediatric department has made timely delivery of intensive care services for critically ill oncologic patients challenging. This in turn has direct implications for the immediate and long-term survival of the child battling with cancer.

The chemotherapy protocol for the treatment of pediatric NHL varies according to the immunophenotype of the malignant cell. It varies from institution to institution which is mainly a reflection of the set-up. in our setup for those patients with lymphoblastic lymphoma, we use high-risk ALL protocol. For all other patients with NHL, we use a locally modified ALCL protocol which was started after experts' opinions and discussion. The major difference from the currently practiced international protocol includes giving low-dose systemic methotrexate, not including targeted therapy like rituximab for those with mature B-cell lymphoma and not modifying the cycle of treatment according to the disease staging and grouping. Even if the protocol lacks high-dose methotrexate it is intensified with other cytotoxic chemotherapy and given for six to seven cycles. In Europe, this protocol without modification is being used only for those patients with anaplastic large cell lymphoma.

This study, therefore, will try to assess early induction treatment-related mortality of children with NHL being treated with modified ALCL99 protocol and the impact of those associated listed above.

1.3 Significance of The Study

More than 90% of patients with NHL usually survive the early treatment phase with full supportive care in the best treatment facilities. Due to all the shortcomings achieving this goal is difficult. In our set-up, there are no published data regarding the early treatment-related complications of childhood NHL treated using different treatment protocols with the currently available supportive care. Therefore, this study is going to assess treatment-related mortality

during the early treatment period of NHL patients treated with locally modified ALCL protocol at TASH. The study also assesses the different factors like patient or disease factors, treatment factors, and availability of supportive care which positively or negatively affect the survival of these patients from early treatment-related toxic death. Even if it is difficult to compare the treatment-related complications with a different setup treating patients with NHL with less intensive or very intensive chemotherapy protocol as compared to ours; it gives an insight to see the feasibility of using the modified ALCL protocol for most of the patients with NHL.

Chapter 2: Literature Review

2.1 Clinical Profile of Non-Hodgkin's Lymphoma

Non-Hodgkin lymphoma affects people of diverse ages, usually in the second decade of life. It seldom affects children under the age of three and is extremely rare in newborns (1% in the Berlin-Frankfurt-Münster [BFM] trials from 1986 to 2002). Except primary mediastinal B-cell lymphoma, childhood NHL typically affects boys at least twice as often as females. In a multicenter study, the male-to-female ratio for Burkitt lymphoma was 3:1. The study used data from International Agency research on cancer, which included 3,403 patients from four continents (excluding Africa). Studies conducted in Tanzania and Egypt have similarly revealed a male preponderance in NHL incidence.(1,20,21)

The presentation pattern of NHL in children and adolescents is heterogeneous, ranging from a single painless enlarged lymph node, an asymmetrical enlarged tonsil, or a benign-looking skin papule, to a potentially fatal oncologic emergency such as spinal cord compression, airway obstruction, and another organ dysfunction brought on by TLS. In contrast to adults, over two-thirds of children with NHL typically exhibit advanced-stage illness, encompassing extra nodal disease involving involvement of the gastrointestinal tract, bone marrow, and central nervous system (CNS). Every subtype of childhood NHL has an impact on therapy and outcomes due to the involvement of the CNS and bone marrow.(2)

The clinical manifestations of various NHL histologic variations vary from one another. When Burkitt lymphoma occurs sporadically, widespread lymphadenopathy and abdominal involvement are the most common presenting signs. In endemic cases of Burkitt lymphoma lesions in many quadrants of the jaw, orbital tumors with or without maxillary disease are typical. Patients suffering from lymphoblastic lymphoma typically have a fast-expanding lymphadenopathy in the mediastinum, which obstructs the airway and bigger arteries. Typically, patients with ALCL have cutaneous lesions that heal on their own, either with or without the involvement of the lymph nodes, bone, and visceral organs. are usually found in patients with advanced illness. At presentation, about two-thirds of the cases had an advanced illness, typically accompanied by systemic signs including fevers.

An investigation on the outcome and toxicity patterns in children and adolescents with NHL was conducted in Canada, involving 164 immunocompetent patients under the age of 18. The head

and neck were the most commonly involved areas in those under the age of fifteen. The most common histological subtype in children was BL, but the most common in teenagers was ALCL. Over 75% of the patients had advanced disease (stage III or IV), with 15% having increased LDH, 38% having B symptoms, 11% having BM involvement, and 9% having CNS involvement (21).

Prognostic markers such as dissemination to the central nervous system and bone marrow are significant, and the degree of involvement differs throughout NHL types in pediatric patients. Compared to other subtypes such as lymphoblastic lymphoma (5%), DLBCL (3%), and ALCL (2.6), Burkitt lymphoma (9%) is more likely to impact the central nervous system (CNS).1, 2. Characteristics of Central Nervous System (CNS) Involvement in Children with Non-Hodgkin's Lymphoma (NHL) and the Diagnostic Utility of CSF Research conducted in China Flow Cytometry in CNS Positive Disease: Out of the 383 children with NHL who were included, 56 (15%) had CNS disease, of which 26 (46%) had Burkitt(22). Of the 1989 individuals under 20 years old with confirmed NHL in another French investigation, 217 (12.8%) tested positive for CNC. 191 (88%) of them had lymphoblastic and Burkitt lymphomas. About 25% of the children in research on the history, clinical features, and therapy of Burkitt lymphoma conducted in various parts of Africa have advanced disease with CNS involvement (18,22).

Prior to diagnosis, patients with NHL may experience acute airway obstruction, spinal cord compression, intussusception/intestinal obstruction, spinal cord compression, superior or inferior vena cava blockage, and problems involving the central nervous system (CNS).[2,6,7]

The BFM group reported that between 25% and 30% of children present with acute abdominal pain caused by an ileocecal intussusception or a right lower quadrant mass. The report also discussed the importance of first laparotomy and second-look surgery in the management of abdominal B-cell NHL. The incidence of tumor lysis syndrome in children with advanced-stage Burkitt's lymphoma/leukemia before and after the introduction of prophylactic usage of urate oxidase was examined in two multicenter studies NHL-BFM90/95, which included 1791 NHL children. Before prophylaxis was introduced, 9.2% of children developed TLS; this number later decreased to 6.2% when prophylaxis was started for all patients (15, 20,26).

Most NHL patients don't have a noticeable abnormality in their peripheral blood count when they first appear. From the University of Nebraska research that included 317 cases and

examined the clinical significance of hematologic markers in individuals with NHL At presentation, 42% of patients had anemia, 6% had leukopenia, 13% had thrombocytopenia, 26% had leukocytosis, and 14% had thrombocytosis. Another study conducted in Pakistan examined the involvement of the bone marrow in children diagnosed with non-Hodgkin's lymphoma. The mean platelet count was 201.9 ± 129.3 × 109 /L, the mean absolute neutrophil count was 4.3 ± 3.2 × 109 /L, the mean total leukocyte count was 9.0 ± 6.5 × 109 /L, and the mean hemoglobin was 10.8 ± 2.7 g/dl. Of the patients, 11.4% had anemia. (23,24).

According to the findings of the FAB LMB 96 study, increased LDH was found in 45% of children with NHL under the age of 15, which was greater than in teenagers between the ages of 15 and 20 (45% v34%; P =.009). More than 50% of children treated at their institution during the study period had increased LDH, which is more than twice the upper limit of normal. Another study on the clinical profile and outcomes of NHL from tertiary institutions in India also revealed this information.(7,25)

2.2: Histopathologic Profile of Non-Hodgkin's Lymphoma

Burkitt lymphoma is the most often diagnosed kind of NHL (40%) based on immunophenotyping, followed by lymphoblastic lymphoma (20%), DLBCL (15%), and ALCL (10%) (2).

In the FAB LMB 96 study, which included 945 patients over the age of 15 and 166 children under the age of 15, Burkitt lymphoma is responsible for 48% and 74% of the cases, respectively.11. Burkitt's lymphoma was the most common NHL subtype (69%), followed by lymphoblastic lymphoma (18.3%), diffuse large B-cell lymphoma (10.6%), and anaplastic large-cell lymphoma (2.1%), in a study from a developing area of Egypt on disease patterns of pediatric non-Hodgkin lymphoma including 142 patients treated over a period of 8 years. Thirty. Burkitt lymphoma (52%) was the most common subtype of NHL in an Indian study that examined the clinicopathologic characteristics and treatment outcomes of children with the disease. ALCL (28%), DLBCL (20%), and other subtypes were also present (26).

A study was done in 5 developing regions of the world which included 24 countries; a review of 4539 cases was done and a comparison of the clinicopathologic profile with the developed countries was done. This region had a significantly lower frequency of B-cell lymphoma (86.6%)

and a higher frequency of T- and natural killer-cell lymphoma (13.4%) compared to the developed world (90.7% and 9.3%, respectively). Also, the developing regions had significantly more cases of high-grade B-cell lymphoma (59.6%) and fewer cases of low-grade B-cell lymphoma (22.7%) compared to the developed world (39.2% and 32.7%, respectively). Among the B-cell lymphomas, diffuse large B-cell lymphoma was the most common subtype (42.5%) in the developing regions.

In a separate Korean study, BL (61.0%) was the most common pathologic subtype, followed by DLBCL (35.4%) and HGBL-NOS (3.6%), which examined the clinical features and treatment outcomes of children and adolescents with aggressive mature B-cell lymphoma. Stage I, II, III, and IV disease was seen in 4 (4.9%), 26 (31.7%), 30 (36.6%), and 22 (26.8%) of the patients, according to the St. Jude classification 32. The most common histologic subtype was BL (53.7%), followed by DLBL (11.4%) and lymphoblastic lymphoma, according to an unpublished report from TASH, Ethiopia. With 47.7% of patients in stage III and 18.8% in stage IV, the majority of patients had advanced disease.

2.3: Rate of Early Treatment-related Mortality among Different Institutions.

The treatment of NHL in children has advanced significantly in recent years thanks to improvements in supportive care, appropriate risk classification, and cytotoxic chemotherapy. For children with early-stage NHL, the 5-year event-free survival (EFS) rates increased from less than 20% to 85% to 95%, and for those with advanced-stage illness, they improved from 70% to 90%.(2)

A significant further development is the reduction in early toxic mortality as a result of TLS. Patients are especially vulnerable to TLS if they have BL or LBL. The problems associated with TLS and uric acid nephropathy are considerably reduced by paying attention to the kidney, monitoring serum levels of electrolyte and uric acid, and implementing an aggressive medication and hydration regimen. Furthermore, several protocols now include cytoreductive prophase, which aids in tumor management without raising the possibility of clinical worsening after treatment initiation. (27)

In the first month of therapy, toxic mortality rates can reach 10%, although in higher-risk LMIC patients, they can reach 30%. Early treatment-related mortality is only 1% to 2% in HICs with the best resources and advances in supportive care, even in cases where current treatment

regimens have significant acute toxicities.2. When using frontline therapy, the cure rate exceeds 90%. But to be cured, a patient must have an accurate and timely diagnosis, undergo rigorous risk assessment, undergo extremely severe chemotherapy, and receive meticulous supportive care. Additionally, patients who live far from the cancer center or cannot afford it must receive logistical support. Lower- and middle-income nations (LMICs) experience far worse outcomes, with cure rates ranging from less than 30% to over 70%.(19,28).

Since 1990, LMICs have been using protocols derived from LMBs. Several reports on the outcome and early toxic death have been released since then. These stories come from nations with radically varied local circumstances when it comes to the availability of medications and supportive care, financial limitations, social unrest, and violence. The five-year EFS rates vary greatly; in reports from Pakistan and Iraq, they are approximately 55%, while in South Africa and Egypt, they are above 85%. Notwithstanding protocol modifications, the outcome is significantly impacted in underdeveloped and socially impoverished nations by the high rate of toxic deaths, which can reach 37%. This is primarily because of tumor lysis syndrome (TLS; 4–11%) and infections (10–23%) that arise during the initial stages of treatment. There is a significant variance among different LMICs in terms of results and early treatment-related death rate of children with aggressive B-cell non-Hodgkin lymphomas treated according to BFM-derived regimens. In a report from Central America covering 386 patients treated with the BFM90 Protocol deaths during induction were 11% and TLS-related mortality was 3%.(28)

Following the administration of LMB-derived regimens for the treatment of children with aggressive B cell lymphoma, a comparable variance was also observed in those LMICs. According to reports from Iraq and Pakistan, which treated 239 and 233 patients using the LMB96 procedure, respectively, 29% and 20% of the induction deaths were toxic. In research from Morocco and Algeria, toxic mortality was recorded in 25% and 15% of the cases, respectively, including 93 and 119 patients treated with the modified LMB protocol34. In Sub-Saharan Africa (SSA), even with modifications to the previous chemotherapy treatment for Burkitt lymphoma, the survival rate is between 30 and 50%. In research conducted in Malawi, the early treatment-related mortality was 33%.(29)

2.4: Causes of Death During the Early Treatment Period

According to a report by the Association of Pediatric Hematology Oncology of Central America, 34 patients (8.7%) died from toxic B cell NHL lymphoma; of these, 21 had infectious complications and 13 from metabolic problems. The report included 405 patients with B cell NHL. According to a comparable study from a tertiary cancer center in India, treatment-related mortality was 27.7%, with uncontrolled infections accounting for 62% of those deaths.(30)

According to a study conducted by Egypt Cairo University Hospital, 84 (or 14.7%) of the 570 patients with pediatric Burkitt lymphoma perished. 84 (14.7%) of the 570 patients registered throughout the research period passed away. The majority of them (94%) had illness in advanced stages (III and IV). 78.6% of patients died while their disease was still active. Tumor lysis syndrome (TLS) (11.9%), disease progression (31%), and septic shock (34.5%) were the primary reasons of mortality. Severe chest infection (6%), multi-organ failure linked to sepsis (6%), pulmonary hemorrhage (2.4%), neutropenic enterocolitis, GVHD, and gut perforation (1.2%) were the other reasons of mortality that were documented. Patients died in prophase in 17 cases (20.4%) and induction in 24 cases (28.5%).(31)

2.5: Predictors of mortality During the early treatment Period

Many predictors of mortality during the induction period and of the overall survival of children with NHL have been described in many works of literature. Several factors have been shown to impact survival among patients with NHL. In resource-rich settings, these have included the tumor stage, bulk and histopathologic type, age, serum lactate dehydrogenase (LDH) level, performance status, and the number of nodal and extra nodal sites involved. Receipt of both chemotherapy and supportive therapy (e.g., Granulocyte colony-stimulating factor, G-CSF) has also influenced treatment outcomes. In resource-poor settings, factors predictive of worse survival include older age, higher tumor stage, high LDH levels, and low hemoglobin concentration(32).

Toxic fatality rates during the first month of therapy can reach 10% in low- and middle-income nations and up to 30% in higher-risk patients. Delay in diagnosis is a major contributing factor to treatment-related deaths or early illness deaths. Individuals with delayed diagnosis typically have more severe disease, increased risk of TLS, concomitant infections, malnourishment, and an increased chance of early toxic death. From a study done in South Africa, Cap Town including

163 patients with lymphoma a diagnosis delay of more than 6 weeks in children suspected of TB, HIV in a setting where both TB and HIV are endemic was associated with advanced-stage disease and related mortality. (32,33)

Toxic fatality rates during the first month of therapy can reach 10% in low- and middle-income nations and up to 30% in higher-risk patients. Delay in diagnosis is a major contributing factor to treatment-related deaths or early illness deaths. Individuals with delayed diagnosis typically have more severe disease, increased risk of TLS, concomitant infections, malnourishment, and an increased chance of early toxic death. According to a study conducted in Cape Town, South Africa, which had 163 patients with lymphoma, children who were suspected of having TB or HIV were found to have a diagnosis delay of more than six weeks in an environment where both diseases are widespread. This delay was linked to advanced-stage disease and consequent mortality.(34)

A case-control study was done in Mexico in children with ALL predictor effects of malnutrition during the induction-to-remission phase of the treatment involving 91 children. It was found that the chance of dying during the initial phase of the treatment was 2.6 times higher (confidence interval 95%: 0.55-11.89) in undernourished children with ALL than in those children with normal nourishment status. The risk of death increased with the severity of undernourishment ($p = 0.04$).(35)

All patients under the age of eighteen who received treatment for B-NHL using the FAB/LMB 96 protocol at a tertiary cancer hospital in India between January 2011 and January 2020 were included in this retrospective single-center cross-sectional analysis. 47 patients who were treated using this technique were retrieved. The 2-year overall survival (OS) and event-free survival (EFS) for the entire cohort were 72.8% and 73.4%, respectively, with a median follow-up of 20 months. Out of the 13 deaths in total, 8 (61.5%) were related to therapy. Sepsis caused by multi-drug resistance organisms accounted for almost all treatment-related deaths (7/8; 83.3%). The study's findings were similar to those from low- and middle-income nations, where infections are among the leading causes of death.(36)

In general, high survival rates require intensive chemotherapy to produce the greatest anti-lymphoma effect. High-dose methotrexate, alkylating agents, anthracyclines, vincristine, glucocorticoids, and intrathecal methotrexate at doses that cause severe neutropenia, lymphopenia, thrombocytopenia, and mucositis are among the intense block regimens used in

HIC. These patients require intensive supportive care, which includes managing infection, bleeding, drug-specific toxicities, and malnourishment. Patients typically experience opportunistic infections and significant aplasia, which call for quick access to intense life support. Lower dose regimens are the sole option because applying this intense method would not be possible in many low-income countries (LIC) due to several obstacles that must be overcome at every stage of the process. According to the NHL-BFM-95 trial, methotrexate infusions lasting less than 24 hours were less hazardous, and numerous LMIC facilities.(8,37,38)

An Indian study examined how socioeconomic status affected the course of ALL in low- and middle-income countries. Socioeconomic status was found to have a statistically significant correlation with the survival of childhood ALL after classifying the families as "Good" if they could afford the treatment costs, "Fair" if they could only contribute a portion of the costs, and "Poor" if they were unable to pay any fees. When Arigela et al. looked at how insurance-based healthcare systems and treatment compliance affected everyone's results, they discovered that patients whose families had insurance coverage fared better overall.(39,40)

An investigation of the impact of health insurance status on pediatrics non-Hodgkin lymphoma conducted in Kenya corroborated the results of these studies. NHL diagnoses were made for 63 people in all. After early death (14), disease progression and relapse (22%), and treatment abandonment (35%), the most prevalent treatment failure was identified. 49 (73%) of these 62 kids were uninsured at the time of diagnosis, while 17 (27%) of them did. Stages III and IV were diagnosed in uninsured children (90%) more frequently than children who had insurance (62%), out of the 44 cases for which a disease stage was recorded. If a kid had insurance at the time of diagnosis, the most likely outcome was event-free survival; if not, the most likely outcome was treatment dropout.(48)

Chapter 3: Objectives of The Study

3.1: Primary Objective

This study aims to evaluate the mortality and associated variables of children with non-Hodgkin's lymphoma who get therapy at Tikur Anbesa Specialized Hospital as per the modified ALCL protocol between March 2023 and June 2024.

3.2: Secondary Objectives

- To describe the demographic, clinical characteristics, and pathologic pattern of children with NHL.
- To describe the pattern of different oncologic emergencies in those children with NHL.
- To assess and characterize the different treatment-related complications during the early treatment period.
- To identify factors affecting the early treatment outcome.

Chapter 4: Method and Materials

4.1: Study Setting

The study was conducted in TASH, Department of Pediatrics and Child Health, Addis Ababa, Ethiopia. TASH was established in 1974 and is the teaching hospital of the School of Medicine, School of Pharmacy, School of Public Health, and School of Allied Health Sciences. It is also the largest referral hospital in Ethiopia with over 700 beds and serves as a training center for undergraduate and postgraduate medical students, dentists, midwives, pharmacists, medical laboratory technologists, and radiology technologists. The Department of Pediatrics and Child Health is one of the specialty units at TASH which includes a pediatrics orthopedics ward, one NICU, one PICU, one ROPD, and different referral clinic programs in CHS. It consists of one pediatrics emergency ward, four admissions wards including a pediatrics orthopedics ward, one NICU, one PICU, one ROPD, and different referral clinics. The pediatric haemato-oncology ward has 26 beds in TASH 16 beds in the cancer center near Amistegna police station and 20-25 beds in the emergency room. The activity is currently run by three Pediatric Heamato-oncologists and eight Fellows.

The unit is currently running a fellowship program under Addis Ababa University (AAU) with the support of the ASLAN project. The outpatient clinic gives daily services to more than 800 patients every month. The unit also has one Data manager who works on the cancer registry and one Counseling psychologist who gives psychosocial support. The unit also has two support groups giving psychosocial and financial support to the patients namely Tesfa Addis Parental and Childhood Organization (TAPCO) and Mathiwos Wondu Ye-Ethiopia Cancer Society (MWYECS).

4.2: Study Design

Hospital-based prospective cohort epidemiological study design was used.

4.3: Study Period

This study was conducted in Tikur Anbessa Specialized Hospital Pediatric Hematology-Oncology unit in a period between March 2023 and June 2024.

4.4: Patient Eligibility

Initially, 59 patients with a diagnosis of NHL were enrolled in the study. From these 9 patients were ineligible and excluded from the study due to death before starting chemotherapy, and treatment with other non-ALCL protocols like patients with lymphoblastic lymphoma Finally, data from 50 patients were collected and analyzed.

4.5: Sample Size Determination

Due to the rareness of the disease and the short study period; All patients diagnosed with NHL were selected and enrolled during the study period fulfilling the inclusion criteria.

4.6 Inclusion and Exclusion Criteria

4.6.1 Inclusion criteria

- All newly diagnosed patients below 15 years of age with a confirmed diagnosis of non-Hodgkin's lymphoma treated according to the locally modified ALCL protocol were included in the study.

4.6.2 Exclusion criteria

- Patients with lymphoblastic lymphoma treated as High-risk ALL
- Suspected or confirmed NHL patients died or left against medical advice before starting chemotherapy
- Patients with confirmed NHL treated with non-ALCL99 protocol
-

4.7 Study Variables

4.7.1 Dependent Variable

- Early treatment-related death and Induction survival

4.7.2: Independent Variables

- Sociodemographic data: age, sex, address, residence, religion, birth order
- Patient and disease-related factors: Histologic sub-type, major presenting symptom, nutritional status, tumor bulk, LDH, albumin, Hgb, stage/group, presence of oncologic emergency.
- Treatment-related factors: Infectious complications, typhlitis, mucositis, hematologic toxicities.
- Treatment Institution-related factors: availability of ICU bed on time and availability of blood product.

4.8: Data collection and measurements

4.8.1: Data collection measurements

A structured questionnaire was used to collect the data from the patient's chart and the caregiver. The questionnaire had two parts. The first examines the baseline characteristics of the patients and the disease. The second part had a daily assessment tool to collect the data on their daily clinical conditions and laboratory results. The data sheets were filled every day until the end of the B1 phase or until death from any cause whichever comes first. The questionnaire was piloted and revisions were made accordingly.

4.8.2: Data Handling

The collected data was checked by the investigator for cleanliness and completeness. Patient records with incomplete data were excluded. After the quality check, data were entered into SPSS statistical software.

4.8.3: Data Quality Assurance

After collecting data Primary investigator checked its completeness and then coded. The converted soft copy was again cross-checked with the hard copy for neatness, completeness, and consistency before any statistical analysis was performed.

4.8.4: Data Analysis and Interpretation

After a thorough cleaning and checking for completeness data is entered into the Statistical Package for Social Sciences ver. 25 (SPSS) for subsequent descriptive analysis in terms of mean, frequencies, and percentage when appropriate. The chi-square test was used to assess the association among the variables. Multivariate Cox proportional regression model used to determine individual predictors effect on outcome. Overall induction survival is determined using Kaplan–Meier statistics. Statistical significance was taken for p values of 0.25 for univariant and <0.05 for bi-variant logistic regression tests.

4.9: Ethical considerations

Ethical approval was obtained from the Pediatrics and Child Health Department's Research and Publications Committee of the School of Medicine, College of Health Sciences, and Addis Ababa University. Respondents were informed about the purpose of the study and the information required from them. Participant confidentiality was assured. All participants included in the study will be kept anonymous during subsequent analysis and dissemination of results.

4.10: Dissemination of Findings

The result of the study will be presented on the research defense day and a formal report will be submitted to the DPCH. The research output will also be published in local or international peer-reviewed scientific journals and will be shared with governmental agencies to allow for improvements in access to health services including chemotherapy drugs and essential supportive care.

4.11: Operational Definitions

- **Induction phase-** Time during the initial phase of chemotherapy (prophase, A1, B1) which is given during the 1st 9 weeks.
- **Early Treatment-related mortality:** any death that occurs after starting chemotherapy till the end of induction.
- **Diagnostic Delay-**time gap between initial presentation to time of final diagnosis
- **Definitive treatment delay-** time gap between definitive diagnosis and initiation of chemotherapy.
- **Laboratory TLS- Presence of at least 2 laboratory criteria** (UA>8mg/dl, K+>6meq/dl, phosphorus >4.6mg/dl, Ca2+<7mg/dl).
- **Clinical TLS-** presence of at least one clinical and one laboratory parameter.
- **Uncomplicated febrile Neutropenia:** Febrile neutropenia which resolves within five days of starting treatment
- **Complicated Febrile Neutropenia:** not classified as uncomplicated Febrile Neutropenia.

Chapter Five: Results

Sociodemographic Characteristics of Children and Their Caregivers

The analysis comprised fifty (n=50) children diagnosed with NHL. The age range at diagnosis was 2–9 years, with a mean of 5 years. With a male-to-female ratio of 1.5:1, the majority of the children (n=30) were male (Table 1). Most of the children came from Oromia region (44%), and most of them were Orthodox Christian (48%), and Muslim (28%) by religion. The primary caregivers were only the parents, and in 38% of the cases, both of them were the caregiver. A third of caregivers (34%) were farmers, while about 32% of caregivers are literate. Figure 1. Eighty-two percent of the families had health insurance via the community.

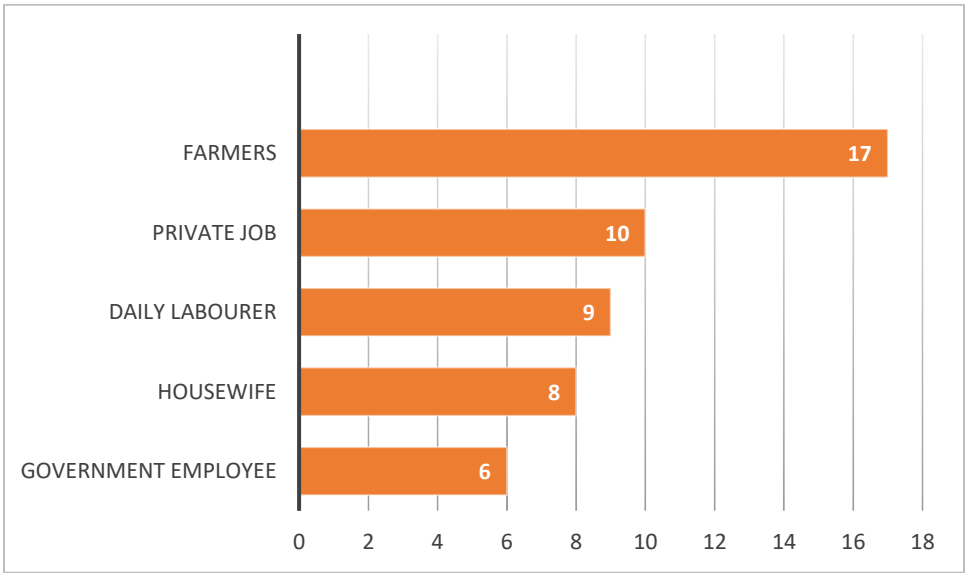

Figure 1- Occupation of the primary caregiver in children with NHL

4.11 Clinical presentation of Children with NHL

Among the clinical presenting symptoms, fever, sweats at night, and weight loss were the most common (82%), followed by abdomen swelling (74%) and neck swelling (26%). On physical examination, around 75% of the patients had localized or widespread lymphadenopathy along with abdominal swelling. When they were presented, one-third of the patients had severe acute malnutrition (SAM). The percentage of children with serum lactate dehydrogenase values

between 500 and 999 and 1000 u/dl, respectively, was about 26% and 60%. Over half of the patients had hyperuricemia, and 26% of the youngsters had moderate to severe hypoalbuminemia(table 1).

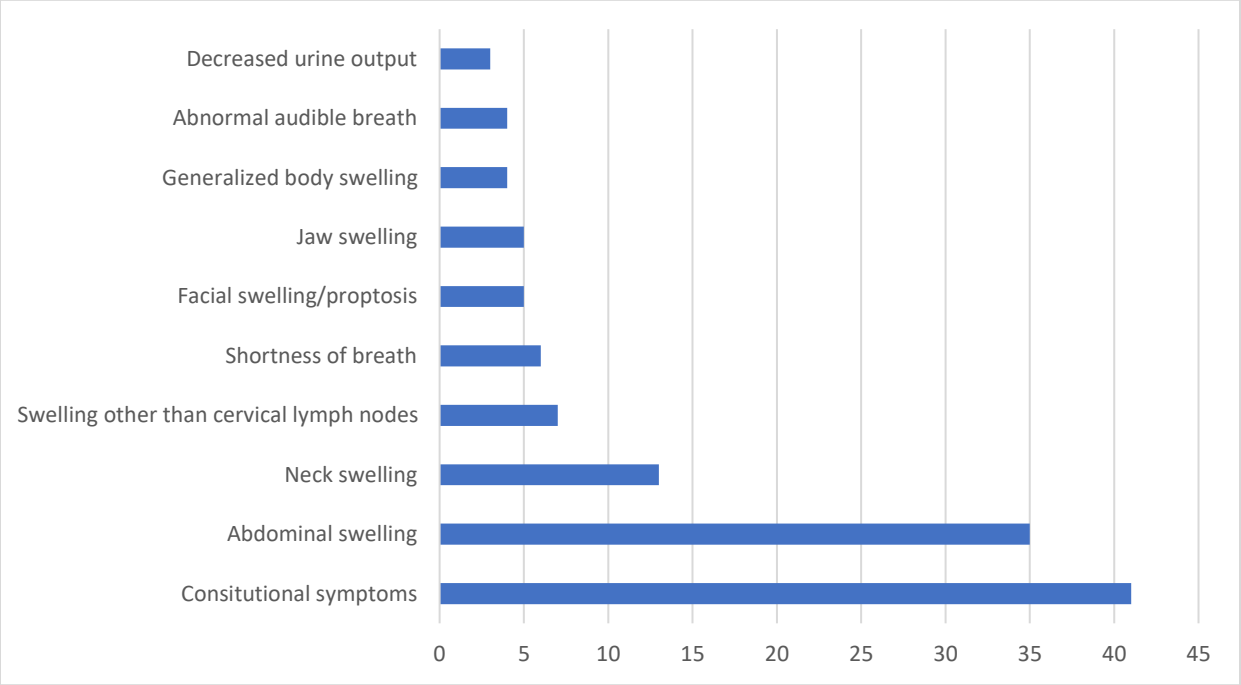

Figure2 - Major presenting complaints in children with NHL

Table1-Initial physical findings and important investigations

Variables	**Number**	**percent**
Physical findings at presentation to TASH		
Wasting (Severe Acute Malnutrition)	17	34
Facial/jaw swelling	7	14
Lymphadenopathy	36	72
Respiratory Distress	5	10

Hepatosplenomegaly		8	16
Abdominal mass		37	74
Pallor		13	26
Laboratory Investigations			
WBC Counts	WBs < 4500	6	12
	Normal WBCs	36	32
	WBCs > 11,500	8	14
Hgb	Normal for age	28	56
	Low for age	22	44
Platelet counts	(>450,000)	26	52
	150000 -450000	19	38
	<15000	5	10
LDH Level	< 500	7	14
	500-999	13	26
	>1000	30	60
Uric Acid	Normal(<8mg/dl)	28	47
	Hyperuricemia(>8mg/dl)	31	53
Serum Albumin	Normal	9	18
	Mild hypoalbuminemia (3-3.5 g/dl)	28	56
	Moderate hypoalbuminemia (2-3 g/dl)	10	20
	Severe hypoalbuminemia (<2 g/dl)	3	6

Diagnostic Investigations, metastatic work-up, histologic diagnosis and staging

The diagnosis of NHL was confirmed with imaging and biopsy in 82% of the cases and immunophenotyping with IHC was done for 8(16%) of the patients. As part of the metastatic work-up, more than 90% of the patients underwent evaluations of their CSF and bone marrow. Forty percent of the patients had Burkitt lymphoma, and over half (54%) had high-grade NHL of

undetermined subtypes (Figure 2). Most of the children presented with an advanced-stage disease from which stage III group B account for 86%, and stage IV group B (8%) at diagnosis.

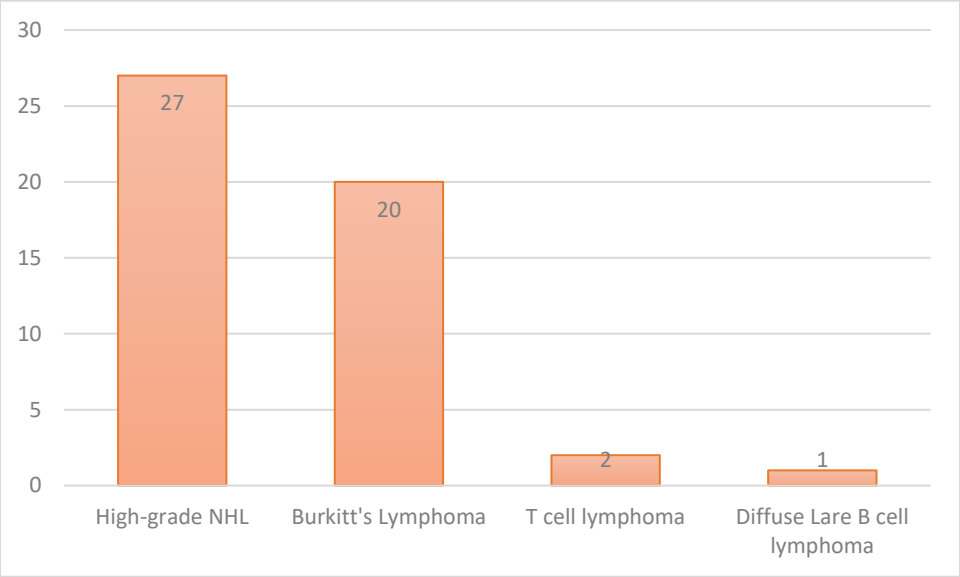

Figure 3- Histological subtypes of NHL (n=50)

Oncologic Emergency at Presentation to Hospital

TLS was the most frequent oncologic emergency found at presentation (56%), followed by infections (32%) and upper airway obstruction (14%) (table 3). Just 25% of them were able to receive ICU treatment, even though one-third of them needed to be admitted (figure 4).

Table 2- Oncologic Emergencies at presentation to hospital

Oncologic Emergency at Presentation			
Variables		**Number**	**percent**
TLS	Lab TLS	28	56
	Clinical TLS	4	8
Superior Mediastinal Syndrome		4	8
Upper airway Obstruction		7	14
Acute Abdomen		6	12
Severe Infection		16	32

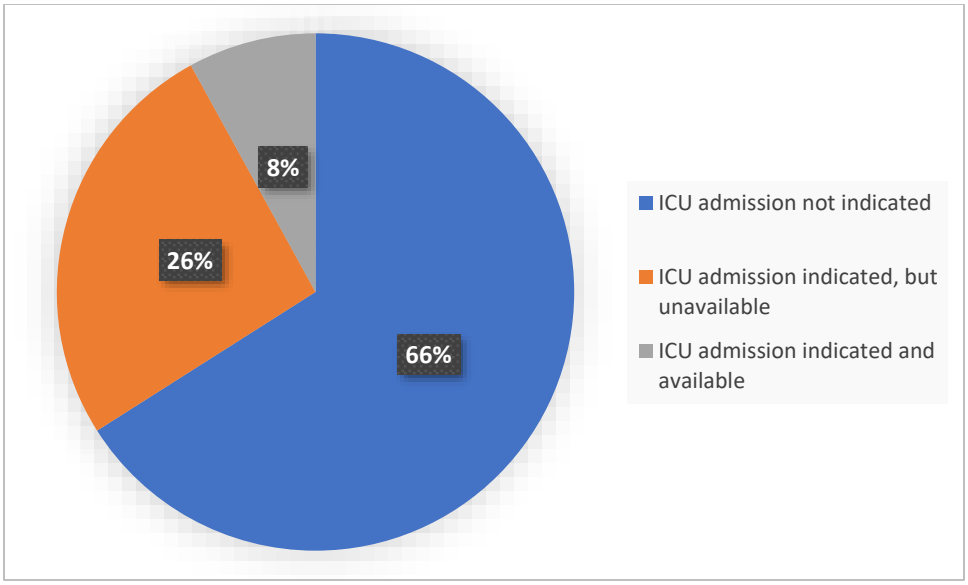

Figure 4- Needs for ICU care and ICU Availability

The average interval between diagnosis and presentation was 42 days, with a range of 12 to 120 days. Approximately 76% of the patients began chemotherapy within a week of the diagnosis.

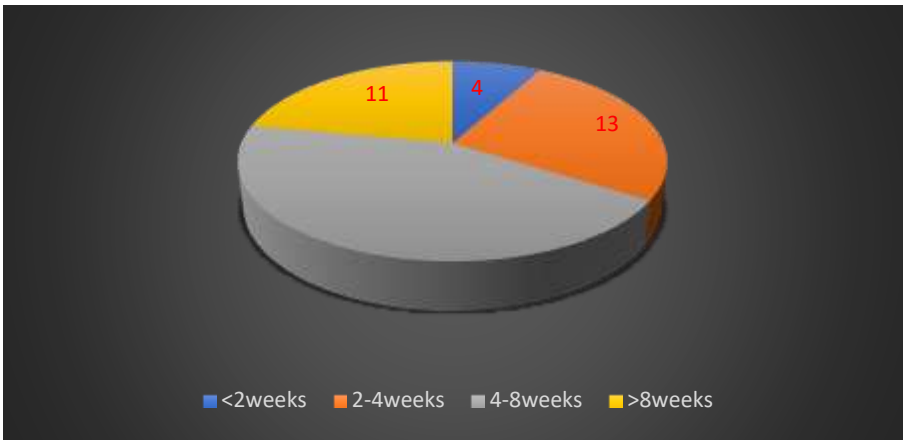

Figure 5 – Diagnostic Delay in Weeks

Acute treatment-related Complications and Major events

During the three phases of induction chemotherapy, 46% and 40% of them develop complicated febrile neutropenia once and twice respectively. During this course of chemotherapy, more than two-thirds of them had grade 3 mucositis, and 40% of them developed grade 4 mucositis. Around 60% of the patients develop radiologically confirmed neutropenic enterocolitis(typhlitis) from which 42% of them had it during both the A1 & B1 phases. From the hematologic toxicity, 90% and 88% of the patients develop severe anemia and thrombocytopenia requiring blood and platelet transfusion respectively. The requested blood products (Platelet, FFP) were not available

in 36 & 24% of the cases. At the end of the induction phase of chemotherapy (Prophase, A1 & B1) there was 12(24%) mortality.

Table3- Treatment-related morbidities and major events

Treatment-Related Morbidities and Events			
Variables		**Number**	**Percent (%)**
Infection	uncomplicated febrile neutropenia (Once, Twice)	(9,1)	(18,2)
	Complicated Febrile neutropenia (Once, Twice)	(23,20)	(46,40)
	Episodes of non-neutropenic febrile illness	7	14
Episodes of G-4 mucositis (once, twice)		(20,1)	(40,2)
Episodes of G-3 mucositis (Once, twice)		(23,11)	(46,22)
Typhlitis (Once, twice)		(21,9)	(42,18)
Severe Anemia Requiring Transfusion (available, not available in >50% of the time)		45(42,3)	90(84,6)
Severe thrombocytopenia requiring Platelet transfusion (available, not available in >50% of the time)		44(26,18)	88(52,36)
Bleeding requiring FFP transfusion (available, not available in >50% of the time)		29(17,12)	58(34,24)
Events(death)		12	24

Factors associated with Induction Mortality

Six of the twenty-five variables that underwent bivariable analysis and had p-values less than 0.05 were considered as potential candidates for the multivariable logistic regression model (Table 2). Hosmer-Lemeshow goodness of fit was used to assess the model's fitness. At a p-value of less than 0.05, it was discovered that there was just one variable in the final model that had an independent and statistically significant association with increased induction mortality. Before beginning chemotherapy, patients with severe infections had five times higher odds of dying than those without (AOR,5.2, P=0.05).

Table 4 Bi-Variable and multi-variable logistic regression analysis of factors associated with early induction mortality among children and adolescents with Non-Hodgkins Lymphoma Treated according to the locally modified ALCL Protocol at TASH

Variables		Events		COR (95%CI)	P value	AOR (95%CI)	P-Value
		Death	Censored				
		No (%)	No (%)				
Age (in years)	< 5	4(33,3)	17(45)	1	0.487		
	6-10	8(66.6)	21(55)	1.619 (0.416, 6.3)			
Health Insurance	Yes	9(75)	32(84)	1	0.473		
	No	3(25)	6(16)	1.778(0.37,8.55)			
Abdominal Swelling	Yes	6(50)	29(79)	3.625(0.916,14.3)	0.067		
	No	6(50)	8(21)	1			
B Symptoms	Yes	8(66.6)	33(86)	3.3(0.718,15.16)	0.125		
	No	4(33.3)	5(14)	1			
Decreased Urine Output	Yes		12(28)	0.611 (0.05,7.4)	0.69		
	No		36(72)	1			
SAM	Yes	7(59)	15(39.5)	0.4 (0.125, 15.078)	0.25		
	No	5(41)	23(60.5)	1			
Hgb	Normal for age	5(41)	23(60.5)	1	0.25		
	Low for age	7(59)	15(539.5)	2.1(0.574,8.03)			
WBC	low	2	4	1.2(0.13,11)	0.87		
	normal	7	29	2.4(0.476, 12.9)	0.28		
	increased	3	5	1			
Platelet	Low	3	2	0.121(0.015,0.973)	0.047		
	Normal	5	14	0.509(0.116,2.2)	0.37		
	High	4	22	1			
Low Platelet	yes	3	2	2.6(0.98,7)	0.055		
LDH	<500	0	7	1	0.125		
	500-1000	1	12		0.08 0.99		
	>1000	11	19				

Elevated LDH	Present	12	31		0.042		
Albumin	Normal	0	9	1			
	mild	8	20	0.999	0.999		
	moderate	3	7	1.25 (0.099,15.7)	0.86		
	Sever	1	2	1.16(0.074,18.3)	0.913		
Stage/group	Stage 2, group A	0	1	1			
	Stage 3, group B	8	35	0.000	0.16 1		
	Stage 4, group B	3	1	4.3(0.24,77.6)	0.3 0.5		
	Stage 4, Group C	1	1	0.33(0.099,11.9)			
Advanced stage	Stage III and above	12	37	0.266(0.069,1)	0.054		
TLS	Present	8	20	0.556(0.143,2.16)	0.39		
	absent	4	18	1			
Severe infection	yes	8	8	0.133(0.032,0.558)	0.006	0.05(0.002,1.08)	0.05
	No	4	30	1			
ICU	Not Indicated	5	28	1			
	Indicated but not available	6	7	1.8(0.16,21)	0.105		
	Indicated and available	1	3	0.34(0.032,4.8)	0.618		
ICU Availability	indicated	7	10	0.48(0.183,1.257)	0.135		
Diagnostic Delay	<2weeks	2	2	1			
	2-4 weeks	3	10	0.375(0.035,4)	0.418		
	4-8 weeks	4	18	1.25(0.196,8)	0.813		
	>8 weeks	3	8	1.68(0.3,9.35)	0.549		
Definitive treatment delay	<1 week	11	27	1	0.174		
	>1 week	1	11	0.223(0.026,1.94)			
Episode of complicated NF	once	5	17	10.2(0.86,120)	0.066		
	twice	4	18	13.5(1.1,166)	0.042		
	Three times	0	2		0.999		
	none	3	1	1			
Complicated FN	Present	9	38	0.6(0.289,1.2)	0.149		
Typhlitis	Once	5	15	1(0.254,4.5)	0.925		
	Twice	2	9	1.6(0.255,10.1)	0.614		
	None	5	14	1			
Grade 3 mucositis	Once	3	21	10.5(2.14,51.5)	0.004		

	Twice	0	11		0.99		
	None	9	6	1			
Grade 3Mucositis	Present	3	32	0.34(0.224,0.707)	0.002		
Grade 4 mucositis	Once	7	15	0.48(0.13,1.8)	0.286		
	Twice	0	1		1		
	None	5	22	1			
Severe Anemia requiring transfusion	Yes & blood is available	2	24	7.5(1,53.5)	0.044		
	Yes, but blood is not available	5	13	0.7(0.038,14.9)	0.85		
	Not required	5	1	1			
Anemia requiring transfusion	Present	9	38	0.318(0.149,0.845)	0.022		
Severe thrombocytopenia requiring transfusion	Yes & Plt is available	7	35	60(4.5, 797)	0.02		
	Yes, but Plt is not available	2	1	13(1.2,140)	0.035		
	Not required	3	2	1			
Thrombocytopenia requiring transfusion	Present	9	36	0.14 (0.041,0.48)	0.0022		
Bleeding requiring FFP transfusion	Yes & FFP is available	1	16	9.8(1.09, 89)	0.042		
	Yes, but FFP is not available	3	9	1.8(0.38,8.9)	0.446		
	Not required	8	13	1			
Bleeding requiring FFP transfusion	Present	9	36	0.36(0.143,909)	0.031		

Using the Kaplan Meier survival estimate, the mortality/death of children after induction chemotherapy (end of B1) is calculated. Thirty-three of the fifty patients who began chemotherapy finished the induction phase, five stopped the treatment, and twelve died. The majority of deaths happen during the chemotherapy's pre- and A1 phases. Patients with a severe infection had a 5.45-fold increased risk of dying compared to those without a severe illness (HR:5.45; 95% CI:1.63, 18.26).

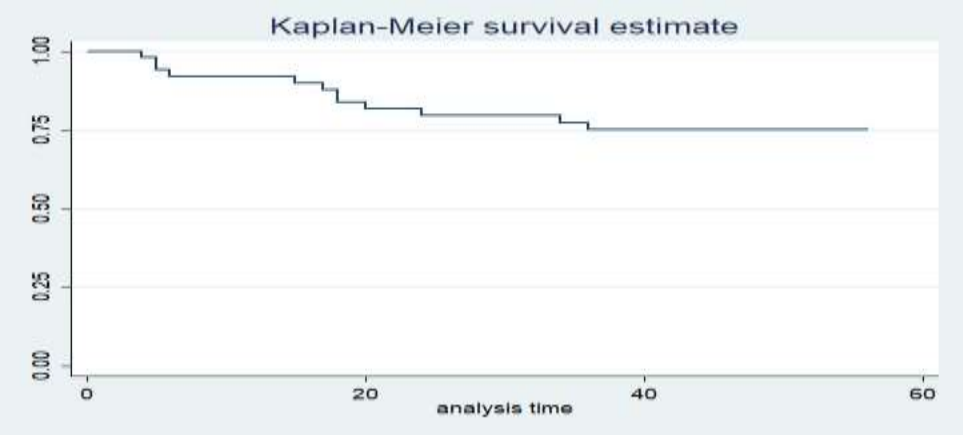

Figure 6. Kaplan Meier survival estimate

Chapter Six: Discussion

Current treatment of pediatric and adolescent non-Hodgkins's lymphoma includes multiple cycles of selected chemotherapy combination intensified with dose and given within short time intervals; CNS-directed therapy to prevent relapse and surgery for a selected group of patients. In addition to the intensive chemotherapy advancement in supportive care and being included in international trials significantly improved the outcome to 85% to 95% for children with early-stage NHL and to 70% to 90% for advanced-stage disease. From the initial studies, the majority of the patients died during the induction phase of chemotherapy while the patient was having the disease burden and the complications associated with the disease. The progressive improved outcome of pediatric NHL was extensively studied in developed and developing countries but there is no published data found from our country. There is also no data describing the mortality during this early induction phase of treatment. (2)

In this Prospective cohort study, 50 patients below the age of 15 years with a diagnosis of NHL were included. The mean age at diagnosis was 5 years and 60% of the patients were in the age range between 5-10 years. More than two-thirds of the patients were male with M: F ratio of 2:1. Similar studies from BFM, Egypt, Tanzania and studies done using the data from international agency research for cancer including 3403 patients show similar age distribution and male predominance at least by a factor of two (1,13,23,24).

Tumors in pediatric and adolescent NHL are frequently found extra nodal and usually confused with other malignant and non-malignant conditions in addition to diagnostic difficulty.in our analysis of 50 patients the commonest being B-symptoms (82%) and abdominal swelling (74%). Similar results were reported by many authors, like in Egypt, Turkey, Malawi, and Mexico; abdominal swelling was a major presenting complaint in 73%,75%, 47%, and 48% respectively (30,23,27).

Due to the unavailability of diagnostic modalities like immunophenotyping cytogenetics and molecular tests; the diagnosis was confirmed only by using imaging and histopathological reports in 82% of the cases and immunophenotyping was done only in 16% of the patients. In more than 90% of the patients' metastatic workup with CSF studies and Bone marrow studies were done. Around half of the patients (54%) were reported as having high-grade lymphoma(unspecified) and Burkitt lymphoma (40%). From the FAB LMB 96 study involving 166 children below 15 years, Burkitt lymphoma accounts for 48%(7). Similar studies from Korea, Egypt and India on the clinic-pathological profile of pediatric and adolescents NHL Burkitt lymphoma accounts for 37%,69%, and 62% of the subtypes respectively. A large study done in 5 developing regions of the world which included 24 countries; a comparison of the clinicopathologic profile with the developed countries was done. the developing regions had significantly more cases of high-grade B-cell lymphoma (59.6%) and fewer cases of low-grade B-cell lymphoma (22.7%) compared to the developed world (39.2% and 32.7%, respectively). This can be partly explained by the fact that there is high malaria and EBV infection in our country even if the true burden of EBV and EBV-related malignancies are not known. A conclusion cannot be made as a significant number of patients (54%) in our study were reported as high-grade NHL (9,30,31,32).

More than 90% of the patients presented as advanced-stage disease (86% stage III, group B,6% stage IV group B) with elevated LDH levels (86%). similar results were reported from previous studies (11,15,27,28,29). These high prevalence rates of advanced presentation in our set-up were possibly related to having voluminous abdominal lymphoma, diffuse LAP, and delayed presentations.

Major life or organ-threatening complications in children with NHL are oncologic emergencies like TLS, airway obstruction, and intestinal obstruction. in the current study, more than half of the patients had TLS and 14% of them had upper airway obstruction. In two multicenter studies NHL-BFM90/95 including 1791 children with NHL on the Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase. before the introduction of prophylaxis 9.2% of children develop TLS, and later drop to 6..2% after starting all patients with prophylaxis.(11,16,42) this significant difference in the prevalence of TLS as compared to our report may be due to the small sample size, advanced stage, and late presentation.

Currently, children and adolescents with NHL except Lymphoblastic lymphoma are treated with intensive chemotherapy according to the recommendations from various study groups like BFM, LMB, and other locally modified protocols. Due to the inadequacy of the supportive care, ICU, and some important medication, we are treating children with NHL by locally modified ALCL protocol. Most patients especially in lower setups usually develop severe therapy-related toxicity and toxic death during the early phases of treatment.

In our study throughout the induction phases which have 3 phases (prophase, A1, B1) 46% and 40% of the patients have complicated febrile neutropenia once or twice correspondingly. Sixty percent of the patients had a diagnosis of neutropenic enterocolitis, and ninety percent of them needed transfusion assistance. After the chemotherapeutic induction phase, the death rate was 24%. Even if a different but related protocol for treating NHL children, the findings of this study are similar to the early treatment outcomes of other LMICs. In a Central American study, 386 individuals who received treatment using BFM-90 produced 11% of protocol deaths that occurred during induction, while 3% of deaths were connected to TLS. In an analogous study from Turkey, In the multi-variant analysis, only the presence of severe infection before starting of chemotherapy has a significant association with induction mortality. many other authors reported that the Advanced stage of the disease at presentation, high LDH, malnutrition, delayed presentation, age, chemotherapy-related toxicity like infection, hematologic toxicity, and lack of community-based insurance have a significant association with induction mortality in low-income countries. The lack of association with other variables in our study may be due to the small sample size. (10,12,39-47).

Chapter 7: Conclusion

This study concluded that the induction phase of treatment resulted in a significantly high death rate (24%) for children and adolescents with NHL who were treated by the locally modified ALCL protocol. The prophase and A1 phase are when most deaths occur. A small sample size may have contributed to the lack of statistically significant associations discovered among the variables connected to induction mortality, with the exception of a severe infection before to starting chemotherapy. Improving the treatment of oncologic emergencies, supportive care, and doing a robust prospective study with an adequate sample size is recommended.

Chapter 8: Limitation of the study

Our study is the first prospective investigation on the mortality of children with NHL associated to early therapy; nevertheless, because of the short study period and limited sample size, it is challenging to draw firm conclusions.

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Annex II: Consent Form

የስምምነት ቅጽ ፡

የጥናቱ የመረጃና ስምምነት ሰነድ

ይህ የመረጃና የስምምነት ሰነድ በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ሕክምናና ትምህርት ክፍል ተኝተው በNon-Hodgkin's lymphoma /የንፍፍት ካንሰር በሽታ ለሚታከሙ ሕጻናትና ልጆች የህክምና ሰነድ፣ ከሚወስዱት መድኃኒት ጋራ ተያይዞ የሚመጡ በሽታ የመቀነስ ፡ ትኩሳት፡ የአፍ መቁሰል ፡ ያለውን ሞት ለማጥናት ለማጥናት የተዘጋጀ ነው።

የጥናቱ መነሻ ሐሳብ እና አላማ

ይህ ጥናት ጥቁር አንበሳ ሆስፒታል በNon-Hodgkin's lymphoma /የንፍፍት ካንሰር በኬሞቴራፒ የሚታከሙ ህፃናት ከበሽታው ጋር ተያይዞ የሚደርስባቸውን ተያያዥ ጉዳት ያጠናል። የጥናቱ አላማ ታካሚዎች ላይ የሚደርሰውን ጫና በመረዳት አስፈላጊው ድጋፍ እና ትብብር የሚያገኙበትን ሁኔታ መፍጠር ነዉ።

ከእርሶ ምን ይጠበቃል?

በጥናቱ ለመሳተፍ ከፈቀዱ ስለእርስዎ የማህበራዊ ሁኔታና ስለ ልጅዎ የጤና ሁኔታ መረጃ ይሰጣሉ።

በጥናቱ ላይ በመሳተፍ የሚያጋጥሙ ስጋቶች

ልጅዎ ወይም እርሶ በዚህ ጥናት በመሳተፋችሁ የሚደርስባችሁ አንዳችም ጉዳት አይኖርም።

ምሥጢር ስለመጠበቅ

የጥናቱ የተሳታፊዎችን መረጃም ሆነ ማንነት በምሥጢር የሚጠበቅ ይሆናል በመሆኑም የተሳታፊዉ ስም በጥናቱ መጠይቅ ላይ አይካተትም።

በጥናቱ ለመሳተፍ ስላለመፈለግ ወይም ተሳትፎን ስለማቋረጥ*በጥናቱ እንዲሳተፉ አይገደዱም። እንዲሁም ተሳትፎዎን በማንኛውም ጊዜ ማቋረጥ ይችላሉ። በመሳተፎ ራስዎን ወይም ልጅዎን በተመለከተ መግለፅ የማይፈልጉት መረጃ ካለ እንዲገልፁ አይገደዱም። በጥናቱ መሳተፍ ባይፈልጉ በልጅዎ የህክምና ክትትል ላይ የሚያሳድረው ምንም ዓይነት ተጽእኖ አይኖርም።

የጥናቱ ጥቅም

ከዚህ ጥናት የሚገኘው መረጃ በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ለሚታከሙ የሕጻናት የካንሰር ህመምተኞች የሚደረገውን ህክምና እና ክትትል ለማሻሻል ይጠቅማል።

በጥናቱ ወቅት ጥያቄ ቢኖሮት

ማንኛውም ጥያቄ ካሎት ከዚህ በታች በተገለፀው የዋና ተመራማሪ አድራሻ በመጠቀም መጠየቅ ይችላሉ።

የስምምነት ሰነድ

ልጁ/ ልጅቱ በዚህ ጥናት እንዲሳተፍ (እንድትሳተፍ) ፈቃደኛ ስለሆኑ ለትብብርዎ በቅድሚያ እያመሰገንን ከበታች በተዘጋጀው ቦታ ላይ እንዲፈርሙ በትህትና እንጠይቃለን።ከዚህ በታች ስምና ፊርማዬ የተገለፀው ግለሰብ ከላይ የተገለፁትን መረጃዎች በማንበብ እና በመረዳት የጥናቱ ተሳታፊ ለመሆን ተስማምቻለሁ።

ስም _____

ፊርማ:_____ ቀን፡_____

ዋና ተመራማሪ፡ ዶ/ር ሙሉዓለም ንጉሴ

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Annex II: Study Questionnaire

TREATMENT RELATED MORBIDITY AND MORTALITY IN CHILDREN WITH NON-HODGKIN'S LYMPHOMA TREATED AT TASH WITH ALCL99 PROTOCOL: PROSPECTIVE COHORT STUDY.

Instructions – Please take your time to carefully complete the information below
Date __/___/___ IC No. _____ Phone No. _____

No.	**Part I - Socio-demographic Variables of the Patient**	
1.	Age of child at diagnosis	_____years _____ months
2.	Sex of the child	1. Male 2. Female
3.	Birth order of the patient	1. First 2. Second 3. Third 4. fourth 5. specify
4.	Family size (Total number of children)	
5.	The region from which the child referred	1. Amhara 2. Oromia 3. SNNPR 4. Tigray 5.Addis Ababa 6. Somalia 7. Afar 7. Others (specify) ___
6	Distance From TASH	In Hours _____
7.	Religion	1. Orthodox Christian 2. Muslim 3. Protestant 4. Catholic 5. Other (specify) ___
No.	**Part II - Family's and Primary caregiver Informations**	
1.	Primary Care giver	1. Mother 2. Father 3. Both parents 4. Adult relative 5. Non-relative adult 6. Orphanage If Not, Parents state why. _____
2.	Primary caregiver's highest level of education.	1. No formal education 2. Can read and write 3. Primary education (attended grades 1-8) 4. Secondary education (attended grades 9-12) 5. College level education
3.	Occupation of the care takers	Father_____ Mother_____
4.	Does the family have health Insurance?	1. Yes 2. No

No.	Part III- Clinical Profile and Related history of the patient	
1.	Duration of illness in days	
2.	Major Presenting Symptoms (you can choose more than one)	1. Abdominal swelling 2. Neck swelling 3. Swelling over the face, proptosis 4. Jaw swelling 5. Generalized body swelling 6. Fever, night sweating, weight loss 7. shortness of breath, cough 8. Abnormal breath sound 9. Decreased urine output 10. Abnormal body movement, decreased level of consciousness 11. Bleeding 12. Bone pain 13. Skin lesion 14. Other (specify) _____
3.	Initial Physical Examination	1. Vital sign -BP ( ) PR ( ) RR ( ) To ( ) 2. Anthropometry Wt___Ht/L ___ MUAC___ HC___ (Normal underweight MAM SAM Stunted) 3. Facial swelling (Yes No) 4. swelling over the jaw (Yes No) 5. LAP (local diffuse) 6. Sign of superior mediastinal syndrome (Yes No) 7. Sign of SVC Obstruction ((Yes No) 8. Plural effusion ((Yes No) 9. Arrythmia (Yes No) 10. HSM (Yes No) 11. Abdominal mass (Yes No) 12. Testicular mass (Yes No) 13. Pallor (Yes No) 14. skin lesion (Yes No) 15. CNS - Seizure (Yes No) - Depressed level of consciousness (Yes No) - Lateralizing sign (Yes No)
10.	Date of initial visit to the nearby health care facility (DD/MM/YY)	
11.	**Date of referral to TASH**	

12.	**Source of referral to TASH**	1. Health center 2. District hospital 3. General hospital 4. Private clinic/hospital 4.Tertiary referral Hospital 5. Self- referred
13	**Initial diagnosis at referring hospital**	
14	**What treatment was the patient getting before arriving to TASH, and for how long?**	
15	**Major diagnostic Tests done at referring hospital**	
16.	**Date of enrolment to TASH**	
17	**Oncologic emergency at presentation**	1. Yes 2. No
18	**If yes, which oncologic Emergency**	1. Superior mediastinal syndrome 2. Upper air way obstruction 3. Massive pericardial effusion 4. Massive plural effusion 5. Arrythmia 6. Abdominal compartment syndrome 7. TLS 8. AKI 9. Increased ICP 10. Spinal cord emergency 11. Sever infection (specify the focus)
	Treatment initiated for Oncologic emergencies at Emergency ward if yes (Choose)	1. Cytoreductive chemotherapy 2. Steroids 3. Emergency radiotherapy 4. Emergency Surgery 5. Iv antibiotics 6. Oxygen support 7. Hydration 8. Drainage 9. Mannitol 10. Other (specify)
	Need for ICU admission	1. Yes 2. No If yes, specify the indication and availability of ICU bed _____

15.	**Date of presumptive diagnosis**	
16.	**Date of final diagnosis confirmed**	
17.	Gaps between date of final diagnosis and initiation of treatment in days	

No.	**Part IV: Baseline PRETREATMENT Laboratory and Imaging Profile**	
1.	CBC - WBC count _____ ANC _____ ALC _____Hgb/HCT _____ Plt **_____ ESR ----**	
2.	**Uric acid _____** LDH_____ - RFT (Cr ____ BUN (_____) - Serum electrolytes (K_____ Na+_____ Cl_____ Ca_____ Mg_____ P_____) - Liver Enzymes (AST _____, ALT _____ ALP _____) - Liver function tests (Albumin_, Bilirubin(T/D) _____, PT ____, PTT ____ INR ____)	
3.	Others - HBsAg - Neg / Pos HCV antibody - Neg / Pos PICT- Neg / Pos	
4.	Imaging done (write the conclusion)	1. Ultrasound_____ 2. Chest X-ray_____ 3. CT scan_____ 4. MRI_____
5.	Histopathological confirmatory testes (write the conclusion)	1. Biopsy: _____ 2. Image guided FNAC: _____ 3. Bone marrow aspiration and biopsy: _____ 4. CSF cytology: _____ 5. Immunohistochemistry: _____
6.	**Diagnosis (including the stage and group)**	
7.	**Date of Initiation of Chemotherapy**	
8.	**Time gap(in days) between initial presentation and chemotherapy initiation(write reason for the delay)**	

parameter	0	1	2	3	4	5	6	7	8	9	10
WBCs											
ANC											
Hgb											
PLT											
Albumin/protein											
Cr											
LDH											
Uric acid											
Serum electrolytes											
LFTS											
CIN											
Febrile neutropenia											
Culture positive(P), Negative(N), Not done (ND)											
Antibiotics needed (yes/no…. Y/N)											
Ceftriaxone/gentamycin (R, A, NA)											
Cefepime (R, A, NA)											
Vancomycin (R, A, NA)											
Meropenem/piperacillin Tazobactam (R, A, NA)											
Cipro floxacillin (R, A, NA)											
Metronidazole (R, A, NA)											
Amphotericin/voriconazole (R, A, NA)											
Acyclovir (R, A, NA)											
Analgesics/ Antipyretics 1*											
Mucositis (Grade 1-4)											
Typhilitis											
Major Bleeding (WHO Grade 3 and 4)											
Kept NPO											
transfusion required (B, P, FFP), Availability (A, NA)											
Albumin Transfusion (R, NR), if Required (A, NA)											
Malnutrition Rx											
Missed chemotherapy											

GCSG (Dose)											
ICU Admission (R, NR), If required (A, NA)											
TMP-SMX PROPHYLAXIS											
Died/alive (D, A)											
If Died, time of death (W, Wn, D, N)											
End of prophase Response Assessment (US, CXR) Note- if prophase is repeated, please fill all the above follow-up parameter for the 2nd prophase											

Part VI: Treatment Profile

Diagnosis: _____ Regimen/protocol: ALCL 99 Weight ____Height____BSA___ Phase /Cycle of Chemotherapy: Prophase Dose reductions Yes ☐ No ☐

Daily Assessment tool

R= Required A= Available NA= Not available B=Whole blood or packed RB P=Platelet F=FFP, AF= Can Afford NAF= Couldn't afford
W= Working day Wn = Weekend D=Daytime N=Nighttime
If Culture positive, Include the etiology and Drug sensitivity Pattern

1* - 1- Paracetamol PO 2.Iv paracetamol 3. Ibuprofen 4. Morphine PO 5. IV morphine 6. Diclofenac 7. Others (Specify)

parameter	0	1	2	3	4	5	6	7	8	9	10
WBCs											
ANC											
Hgb											
PLT											
Albumin/protein											
Cr											
LDH											
Uric acid											
Serum electrolytes											
LFTS											
CIN											
Febrile neutropenia											
Culture positive(P), Negative(N), Not done (ND)											
Antibiotics needed (yes/no…. Y/N)											
Ceftriaxone/gentamycin (R, A, NA)											
Cefepime (R, A, NA)											
Vancomycin (R, A, NA)											
Meropenem/piperacillin Tazobactam (R, A, NA)											
Cipro floxacillin (R, A, NA)											
Metronidazole (R, A, NA)											
Amphotericin/voriconazole (R, A, NA)											
Acyclovir (R, A, NA)											
Analgesics/ Antipyretics 1*											
Mucositis (Grade 1-4)											
Typhilitis											
Major Bleeding (WHO Grade 3 and 4)											
Kept NPO											
transfusion required (B, P, FFP), Availability (A, NA)											
Albumin Transfusion (R, NR), if Required (A, NA)											
Malnutrition Rx											
Missed chemotherapy											
GCSG 3*											
ICU Admission (R, NR), If required (A, NA)											
TMP-SMX PROPHYLAXIS											

Died/alive (D, A)											
If Died, time of death (W, Wn, D, N)											
parameter	11	12	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
WBCs											
ANC											
Hgb											
PLT											
Albumin/protein											
Cr											
LDH											
Uric acid											
Serum electrolytes											
LFTS											
CIN											
Febrile neutropenia											
Culture positive(P), Negative(N), Not done (ND)											
Antibiotics needed (yes/no…. Y/N)											
Ceftriaxone/gentamycin (R, A, NA)											
Cefepime (R, A, NA)											
Vancomycin (R, A, NA)											
Meropenem/piperacillin Tazobactam (R, A, NA)											
Cipro floxacillin (R, A, NA)											
Metronidazole (R, A, NA)											
Amphotericin/voriconazole (R, A, NA)											
Acyclovir (R, A, NA)											
Analgesics/ Antipyretics 1*											
Mucositis (Grade 1-4)											
Typhilitis											
Major Bleeding (WHO Grade 3 and 4)											
Kept NPO											
transfusion required (B, P, FFP), Availability (A, NA)											

Albumin Transfusion (R, NR), if Required (A, NA)											
Malnutrition Rx											
Missed chemotherapy 2*											
GCSF(Include the dose)											
ICU Admission (R, NR), If required (A, NA)											
TMP-SMX PROPHYLAXIS											
Died/alive (D, A)											
If Died, time of death (W, Wn, D, N)											
End of A1 Response assessment (CT)											

Diagnosis: _____Regimen/protocol: Modified ALCL 99

Weight ____Height____ BSA _____

Phase /Cycle of Chemotherapy: A1 or B1 Dose reductions Yes ☐ No ☐

Daily Assessment tool

R= Required A= Available NA= Not available B=Whole blood or packed RB P=Platelet F=FFP,
AF= Can Afford NAF= Couldn't afford
W= Working day Wn = Weekend D=Daytime N=Nighttime
If Culture positive, Include the etiology and Drug sensitivity Pattern

1* - 1- Paracetamol PO 2.Iv paracetamol 3. Ibuprofen 4. Morphine PO 5. IV morphine 6. Diclofenac 7. Others (Specify)

2* Specify the (Missed chemotherapy) _____

Annex III- NCI HEMATOLOGIC and oral mucositis TOXICITY GRADING

Grading	1	2	3	4	5
Anemia Hgb level(g/dl)	Lower limit 10g/dl	8-10	<8	Life threatening condition	Death
Thrombocytopenia	<LLN-75k	50-75k	25-50k	<25k	
Neutropenia	LLN-1500/ul	1000-1500	500-1000	<500	
Bleeding	Petechial bleeding	Mild bleeding	Require transfusion, severe bleeding	Retinal and cerebral bleeding (fatal bleeding	
Oral mucositis	Asymptomatic, or mild symptom	Moderate pain and ulcer	Severe pain Interfering oral intake	Life-threatening consequence	Death