EVALUATION OF KNOWLEDGE AND PRACTICES ON PHARMACOTHERAPY, DRUG-RELATED PROBLEMS, ANTIEMETIC CONSISTENCY, AND IMPACT ON QUALITY OF LIFE IN NON-HODGKIN'S LYMPHOMA CARE IN YEMEN

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UNIVERSITI SAINS MALAYSIA

2025

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by

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Thesis submitted in fulfillment of the requirements
for the degree of
Doctor of Philosophy

March 2025

ACKNOWLEDGEMENT

First and foremost, all praise and thanks to ALLAH SUBHANAHU WA TA'ALA, for granting me the health, blessing, strength, knowledge, and patience to complete this work. Without His support and guidance, this accomplishment would not have been possible.

I wish to express my sincere appreciation and profound gratitude to my main supervisor, Dr. Hadzliana Zainal. Your endless guidance and support throughout the completion of my dissertation have been invaluable. Your thoughtful insights and expertise helped me overcome many challenges, and through your encouragement, I have gained a new perspective and experience in research. I am truly grateful to have you as my main supervisor.

I am also incredibly grateful to my co-supervisors, Prof. Dr. Syed Azhar Syed Sulaiman, Prof. Doa'a Anwar Ibrahim, and Dr. Nur Hafzan Binti Md Hanafiah, for their unwavering support and guidance throughout this process. Their insightful comments and constructive criticism have greatly contributed to the development and improvement of my research.

To the soul of my dear mother, may Allah have mercy on her, and to my beloved father, may Allah protect him, I extend my heartfelt thanks for their unwavering love and support throughout my life. Their sacrifices have not gone unnoticed, and I am forever grateful for their constant encouragement and understanding. Their love and support have been a source of strength, and I am truly blessed to have them in my life.

I express my profound gratitude and special appreciation to my lovely wife, Maisah Alqutmah, for her support and understanding throughout this journey. Her patience, encouragement, and belief in me have been a constant source of strength and inspiration. She has been my rock and partner in every sense of the word. I extend my heartfelt gratitude to my beloved sons, Alzubair, Albara'a, Rami, Abdulmajeed, and to our newest family member, Laith, for lighting up my life every day with their unending love and support.

No words can sufficiently describe my gratitude to my eldest brother, Esam, and to Dr. Ali and Abdullah, for their never-ending encouragement and continuous support that helped me reach this point. My gratitude extends to my sisters, Ibtisam, Fatima, and Aishah, and to my aunt Bushra, along with all my family members for their ongoing support, encouragement, and assistance. They have always been there for me as a shoulder to lean on, and their love and support have been essential to my success. I am forever grateful to have such an amazing family.

I would like to thank my friends and brothers, Fahmi Al-Ashwal, Mohammed Zawiah, and Abdulsalam Halboup, for their support, encouragement, and companionship throughout my PhD journey. Their friendship and support have been invaluable, providing a sounding board for my ideas, a source of inspiration and motivation, and a reminder to maintain perspective. Special thanks to my friend Faiz Nashwan for his friendship and help during this journey.

I want to express my gratitude and thanks to the workers, patients, and healthcare providers in the NOC and all the oncology centers and units for facilitating the data collection stage. Special thanks to Dr. Mohammed Ali Al Sabri, Prof. Jameel Aldobhani, Prof. Sama Alagbari, Dr. Waleed Al Kassar, Dr. Iyad

Alakhali, and Dr. Abdurahman Albukari for their helping hands and support. Finally, I extend my sincere gratitude to all my friends who supported me during this journey.

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LIST OF ABBREVIATIONS

ABVD	Adriamycin, Bleomycin, Vinblastine, and Dacarbazine
ADRs	Adverse Drug Reactions
AIDS	Acquired Immunodeficiency Syndrome
Ara-C	Cytarabine
BSA	Body Surface Area
BVR	Bortezomib, Bendamustine, Rituximab
CAR-T	Chimeric Antigen Receptor-T cell
CCRT	Concomitant Chemoradiotherapy
CHOP/R-CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone ± Rituximab
CINV	Chemotherapy-Induced Nausea and Vomiting
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CNS	Central Nervous System
CR	Complete Response
CT scan	Computed tomography scan
DDIs	Drug-Drug Interactions
DHAP	Dexamethasone, Cisplatin, and Cytarabine
DLBCL	Diffuse Large B-cell Lymphoma
DNA	Deoxyribonucleic Acid
DRP	Drug-Related Problems
ECOG	Eastern Cooperative Oncology Group
EORTC-C30	European Organisation For Research And Treatment Of Cancer Core Quality Of Life Questionnaire
EPC	Emetogenic Potential Risk Chemotherapy
EPOCH	Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
EQ-5D	EuroQol-5 Dimension

ER	Emergency Room
ESHAP	Etoposide, Methylprednisolone, High-Dose Cytarabine, Cisplatin
ESMO	European Society for Medical Oncology
EWB	Emotional Well-Being
FACT-G	FACT-Lym General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FACT-TOI	FACT-Lym Trial Outcome Index
FACT-TOT	FACT-Lym Total
FDA	Food and Drug Administration
5HT3-RA	5-Hydroxytryptamine-3 Receptor Antagonists
FWB	Functional Well-Being
GCCP	Guideline-Consistent Chemotherapy Prophylaxis Group
GCS	Global Cancer Statistics
GICP	Guideline-Inconsistent Chemotherapy Prophylaxis Group
GP	General Practitioner
HCPs	Healthcare Providers
HEC	High Emetogenic Chemotherapy
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HRQOL	Health-Related Quality of Life
HTLV-1	Human T-cell Lymphotropic Virus-1
hyper-CVAD	Hyper-Fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone
ICE	Ifosfamide, Carboplatin, Etoposide
LDH	Lactate Dehydrogenase Test
LEC	Low Emetogenic Chemotherapy

LYMS	FACT-Lymphomas
MAB	Monoclonal Antibody
MALT	Mucosa Associated Lymphoid Tissue
MEC	Moderately Emetogenic Chemotherapy
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCCP	National Cancer Control Program
NHL	Non-Hodgkin Lymphoma
NK1-RA	Neurokinin-1 Receptor Antagonists
NOC	National Oncology Center
PR	Partial Response
PCNE	Pharmaceutical Care Network Europe Association
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PIM	Potential Inappropriate Medication
PP	Polypharmacy
PWB	Physical Well-Being
OS	Overall Survival
R-GDP	Rituximab, Gemcitabine, Dexamethasone, Cisplatin
RR	Response Rates
SWB	Social/Family Well-Being
β2M	Beta-2 Microglobulin

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PENILAIAN PENGETAHUAN DAN AMALAN FARMAKOTERAPI, MASALAH BERKAITAN UBAT, KEKONSISTENAN ANTIEMETIK, DAN KESAN TERHADAP KUALITI HIDUP DALAM PENJAGAAN LIMFOMA NON-HODGKIN DI YAMAN

ABSTRAK

Limfoma bukan Hodgkin (NHL) adalah kumpulan kanser yang heterogen dengan kadar kejadian yang semakin meningkat di seluruh dunia. Pengurusan farmakoterapi yang optimum adalah penting untuk meningkatkan hasil rawatan dan kualiti hidup pesakit (HRQOL). Namun, dalam persekitaran yang kekurangan sumber seperti di Yaman, kualiti penjagaan NHL mungkin tidak mencapai tahap optimum akibat pelbagai cabaran, termasuk akses terhad kepada sumber, latihan yang tidak mencukupi, dan ketiadaan garis panduan rawatan yang standard. Kajian ini bertujuan untuk menilai secara menyeluruh farmakoterapi NHL di Yaman, dengan fokus pada pengetahuan dan amalan penyedia penjagaan kesihatan, pematuhan garis panduan antiemetik, masalah berkaitan ubat (DRPs), dan HRQOL pesakit. Kajian tinjauan keratan rentas dijalankan bermula daripada Januari 2022 hingga September 2023, dalam kalangan doktor dan jururawat dari lapan pusat dan unit onkologi dan 300 pesakit dewasa NHL di Pusat Onkologi Kebangsaan (NOC) di Sana'a. Pengumpulan data melibatkan soal selidik yang disahkan, temu bual bersemuka, rekod perubatan, carta rawatan, dan soal selidik FACT-Lym. Daripada 77 doktor dan 105 jururawat, 54.3% jururawat dan 66.2% doktor mempunyai pengetahuan yang lemah mengenai farmakoterapi NHL, dengan 83.8% jururawat dan 75.3% doktor menunjukkan amalan yang lemah. Pengetahuan dan amalan kemoterapi meningkat dengan maklumat yang mencukupi dan latihan khusus. Hanya 23.9% daripada 251

pesakit NHL menerima rawatan antiemetik yang konsisten dengan garis panduan NCCN. Faktor-faktor penting yang mempengaruhi pematuhan garis panduan termasuk tempoh rawatan, kitaran kemoterapi, dan faktor risiko pesakit. Di kalangan 279 pesakit NHL, 1870 DRP dikenal pasti, dengan purata 6.7 DRP setiap pesakit, dengan isu lazim termasuk dos yang tidak mencukupi dan kesilapan pengiraan dos. Faktor-faktor yang mempengaruhi termasuk sejarah penyakit, bilangan kitaran rawatan, serta morfologi dan subtipe NHL. Terapi tanpa rituximab, sejarah keluarga dan tempoh rawatan melebihi satu tahun dikaitkan dengan skor HRQOL yang lebih rendah. DRP secara signifikan memperburuk HRQOL pesakit. Kajian ini menyimpulkan bahawa terdapat kekurangan yang ketara dalam pengetahuan dan amalan penyedia penjagaan kesihatan mengenai farmakoterapi NHL di Yaman, kepatuhan yang rendah terhadap garis panduan antiemetik, dan prevalensi tinggi DRPs, yang semuanya memberi kesan negatif terhadap HRQOL pesakit. Menangani isu-isu ini melalui penambahbaikan program pendidikan, pematuhan yang lebih baik terhadap garis panduan, dan pengurusan DRP secara proaktif adalah penting untuk meningkatkan kualiti penjagaan dan penambahbaikan hasil rawatan pesakit NHL di Yaman.

EVALUATION OF KNOWLEDGE AND PRACTICES ON PHARMACOTHERAPY, DRUG-RELATED PROBLEMS, ANTIEMETIC CONSISTENCY, AND IMPACT ON QUALITY OF LIFE IN NON-HODGKIN'S LYMPHOMA CARE IN YEMEN

ABSTRACT

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers with increasing incidence globally. Optimal pharmacotherapy management is crucial for improving treatment outcomes and patient quality of life (HRQOL). However, in resource-limited settings like Yemen, the quality of NHL care may be suboptimal due to various challenges, including limited access to resources, inadequate training, and lack of standardised treatment guidelines. This study aimed to comprehensively evaluated NHL pharmacotherapy in Yemen, focusing on healthcare provider knowledge and practices, antiemetic guideline adherence, DRPs, and patients' HRQOL. Conducted from January 2022 to September 2023, the study included cross-sectional surveys of physicians and nurses from eight oncology centers and units and 300 adult NHL patients at the National Oncology Center (NOC) in Sana'a. Data collection involved validated questionnaires, face-to-face interviews, medical records, treatment charts, and the FACT-Lym questionnaire. Among 77 physicians and 105 nurses, 54.3% of nurses and 66.2% of physicians had poor knowledge of NHL pharmacotherapy, with 83.8% of nurses and 75.3% of physicians showing poor practice. Chemotherapy knowledge and practice improved with adequate information and specialized training. Only 23.9% of 251 NHL patients received antiemetic treatment consistent with NCCN guidelines. Significant factors that influence guideline adherence included treatment duration, chemotherapy cycles, and patients’

risk factors. Among 279 NHL patients, 1870 DRPs were identified, averaging 6.7 DRPs per patient, with common issues being underdosing and dose calculation errors. The Influencing factors included disease history, number of treatment cycles, and NHL morphology and subtype. Non-rituximab therapies, family history and treatment durations over one year were linked to lower HRQOL scores. DRPs significantly worsened patient quality of life. This study concludes that there are substantial deficiencies in healthcare providers' knowledge and practices of NHL pharmacotherapy in Yemen, poor adherence to antiemetic guidelines, and a high prevalence of DRPs, all of which negatively impact patients' HRQOL. Addressing these issues through enhanced educational programs, improved guideline adherence, and proactive DRP management is essential to enhance the quality of care and outcomes for NHL patients in Yemen.

CHAPTER 1

INTRODUCTION

1.1 Background of Cancer

Cancer is a generic term for a large group of diseases that can affect various parts of the body. It's also referred to as malignant tumours or neoplasms, characterised by abnormal cell growth that can spread to other parts of the body (Chisholm-Burns et al., 2022; Dipiro et al., 2020). Cancer cells differ from benign tumours in their ability to invade surrounding tissues and spread to distant organs, a process responsible for most cancer deaths (Khoury et al., 2022). Cancer has a significant impact on life expectancy worldwide, ranking among the leading causes of death and affecting people across all geographic, socioeconomic, and cultural boundaries (Bray et al., 2018). Cancers are broadly classified into five main groups based on the cell type they originate from: carcinomas (from epithelial cells), sarcomas (from connective tissues), leukemias (from blood cells), lymphomas (from lymphocytes), and myelomas (from plasma cells) (Abbas, 2023).

1.2 Lymphomas

Lymphoma is a type of cancer that originates in the lymphocytes, white blood cells vital for the immune system. These lymphocytes are found within the lymphatic system, a network of vessels and tissues that extend throughout the body and play a crucial role in fighting infection and maintaining fluid balance. Because lymphocytes are present in various locations, lymphoma can potentially develop almost anywhere in the body, Figure (1.1) (de Leval & Jaffe, 2020; Dipiro et al., 2020).

Lymphoma is classified into two main types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) (Figure 1.2). The defining feature of HL is the presence of Reed-Sternberg cells, a specific type of abnormal cell not found in NHL. NHL typically exhibits a more unpredictable pattern of lymph node involvement compared to HL (Eichenauer et al., 2018; Dipiro et al., 2020).

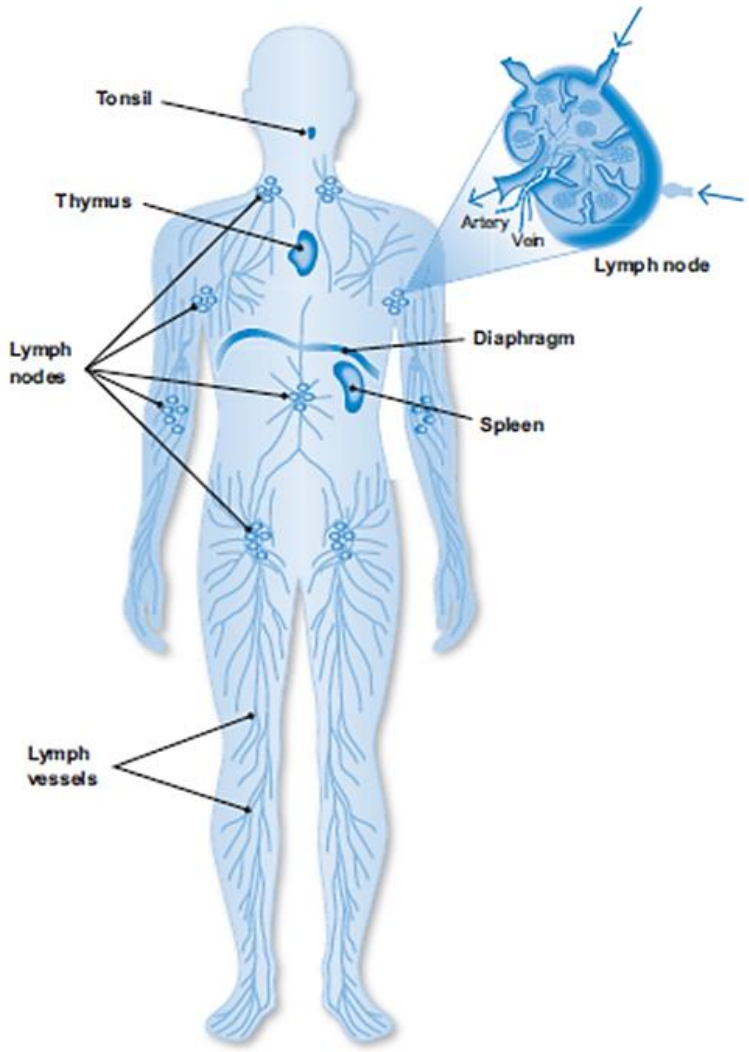

Figure 1.1 Lymphoma

Adapted from: https://lymphoma.org/wp-ontent/uploads/2017/06/Nonhodgkin_Lymphoma_Booklet.pdf. accessed on 22/4/2024.

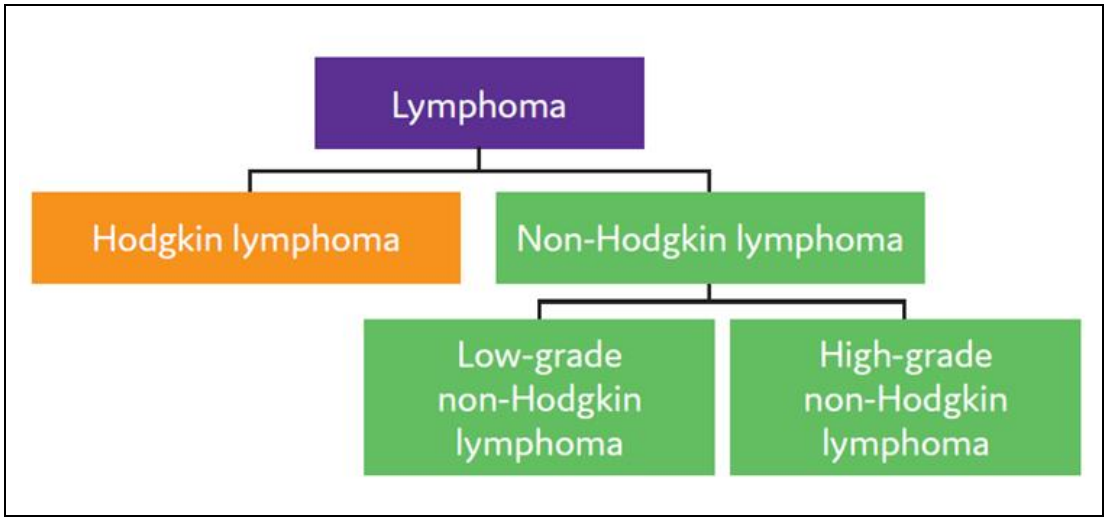

Figure 1.2 Types of Lymphoma

Adapted from: https://lymphoma-action.org.uk/about-lymphoma/what-lymphoma. accessed on 22/4/2024. Lymphoma Action, what is lymphoma?, 30 Jun 2022

1.3 Non-Hodgkin Lymphomas

Non-Hodgkin's lymphoma (NHL), also known simply as lymphoma, is the most common type of lymphoma. It constitutes roughly 85% of all lymphomas, and can occur in people of any age, including children and older adults. However, certain types of NHL, such as Burkitt lymphoma and lymphoblastic lymphoma, are more prevalent in younger individuals (Singh et al., 2020). This cancer encompasses a diverse array of malignancies affecting immune system cells. In NHL, abnormalities arise in the lymphatic system's cells, leading to uncontrolled growth and division, or the failure of old cells to undergo apoptosis as they should (Bayramov & Abdullayeva, 2022; Singh et al., 2020). The classification of NHL involves various clinical subtypes characterised by morphology, immunophenotype, and genetic and clinical features (Dipiro et al., 2020). The WHO classified NHL into T-cell, natural killer (NK-cell), and B-cell types, with B-cell NHLs comprising approximately 85% to 90% of all cases. Among these, diffuse large B-cell lymphoma (DLBCL), which

stands as the most common type of aggressive NHL (rapid-growing) and the most prevalent subtype among over 80 distinct NHL forms, and Follicular Lymphoma, which stands as the most common type of indolent NHL (slow-growing) (Cai et al., 2017; Pratap & Scordino, 2019). Each subtype exhibits unique behavior and responses to treatment (Singh et al., 2020).

NHL is strongly associated with age, gender, and disease stage. The average age at diagnosis is 67, with 57% of cases occurring in individuals over 65. The mean age at death is 76, with 78.5% of deaths also in those over 65. NHL is the seventh most prevalent cancer and the sixth leading cause of cancer-related deaths in the United States, accounting for 4% of all cancer diagnoses (Thandra et al., 2021). Its incidence has risen by 168% since 1975, while survival rates have improved by 158%. NHL is more common in men, individuals over 65, and those with autoimmune diseases or a family history of hematological malignancies. In 2020, NHL caused an estimated 19,900 deaths, representing 3.3% of all cancer-related deaths (Thandra et al., 2021). In addition, the cure rate among patients aged 65 years or older is lower than that among younger patients. It was found that males are more affected than females as well (Ebrahim et al., 2021). The stage of the disease is a dominant factor in predicting the survival and cure rate, where patients with stages I and II (early stage) have a cure rate of 90% to 95%, while patients with stages III and IV (advanced disease) have a cure rate of 60% to 80% (Dipiro et al., 2020).

The incidence of NHL is increasing worldwide, it being the third most common type of cancer in developing countries (Afif et al., 2007; Humam et al., 2016). Furthermore, the Global Cancer Statistics (GCS) for 2018 revealed an alarming escalation in the burden of NHL across many regions, with reported incidences reaching 509,590 cases and resulting in 248,724 deaths. This accounted

for 2.8% and 2.6% of the total incidence and mortality among the 36 cancers studied (Bray et al., 2018). In the United States (US), the incidence of NHL has exhibited a significant uptrend over recent decades, constituting approximately 4% of the overall cancer incidence (Pratap & Scordino, 2019). Moreover, it was estimated 80,550 new cases and 20,180 deaths from NHL in the US in 2023 (Siegel et al., 2023)

1.4 Pathogenesis of Non-Hodgkin's Lymphoma

NHL is a complex condition with various underlying causes. Its pathogenesis involves key mechanisms such as immunosuppression, specifically affecting T-cell function and the loss of control over latent Epstein-Barr virus (EBV) infection, as well as chronic antigen stimulation (Singh et al., 2020). B and T lymphocytes play crucial roles in the immune system, primarily defending against infectious agents. B-cells produce antibodies that can bind to antigens, while T-cells recognize antigens presented by other cells (Yabe & Jeffrey, 2019).

Immunosuppression in various medical conditions increases the risk of NHL. This occurs because T-cell dysfunction, a hallmark of diseases such as HIV/AIDS and organ transplantation, creates an environment conducive to EBV to drive B-cell proliferation and cancer (Meena et al., 2019). In some cases, viruses act as foreign stimulants and can infect normal cells. By integrating viral DNA into the host genome, the virus transforms the cell into a malignant one capable of self-replication. Antigenic stimulation can also lead to a downregulation of the T-cell response, resulting in an immunosuppressive state (Singh et al., 2020).

In up to 90% of NHL cases, the genetic hallmark is chromosomal translocations, often balanced reciprocal recombinations. These translocations, along with additional deletions and mutations, can activate oncogenes or inactivate tumor suppressor genes. Common mutations involve genes like MYC and BCL2, which are critical for cell growth and survival (Sapkota & Shaikh, 2020).

1.5 Signs and Symptoms of Non-Hodgkin's Lymphoma

Signs and symptoms of NHL include:

i) Enlarged lymph nodes: This can occur in the neck, armpits, or groin.

ii) Unexplained weight loss and fatigue.

iii) Fever, night sweats, and chills (combined for related symptoms).

iv) Abdominal or chest pain or swelling: This shows where discomfort is likely.

v) Difficulty breathing or coughing: These are separated to show respiratory problems (Chisholm-Burns et al., 2022; Dipiro et al., 2020)

1.6 Clinical Presentation of Non-Hodgkin's Lymphoma

1.6.1 Nodal lymphoma

Nodal lymphoma in NHL typically spreads to non-adjacent lymph nodes. Abdominal involvement is common, while mediastinal involvement is rare. Cervical lymphadenopathy, characterised by multiple painless, soft nodes unattached to skin or deep tissues, is the most frequent head and neck presentation (Sapkota & Shaikh, 2020).

1.6.2 Extranodal lymphoma

Extranodal NHL frequently involves the head and neck, with Waldeyer's ring, particularly the tonsils, as the primary site. Tonsillar lymphoma often presents with dysphagia, sore throat, and unilateral tonsillar enlargement. Rhinopharyngeal involvement can cause enlarged neck nodes, nasal obstruction, and hearing loss. Salivary gland lymphomas include mucosa-associated lymphoid tissue lymphoma (MALT) of the parotid, follicular lymphomas in intraparotid nodes, and diffuse large B-cell lymphomas (Sapkota & Shaikh, 2020; Singh et al., 2020).

1.7 Risk Factors of Non-Hodgkin's Lymphoma

While most NHL cases occur without identifiable risk factors, certain conditions may increase susceptibility. These include:

i) Immunosuppression: Organ transplants and immunosuppressive medications, such as cyclosporine or tacrolimus, elevate NHL risk.

ii) Infections: Certain viruses (HIV, EBV) and bacteria (*Helicobacter pylori*) are associated with NHL development.

iii) Chemical Exposure: Contact with specific chemicals, such as pesticides, may increase the risk of developing NHL.

iv) Age: The risk of NHL rises with age, with a prevalence in those over 60 years (Zhang et al., 2011).

1.8 Diagnosis and Evaluation of Non-Hodgkin's Lymphoma

The diagnostic process for NHL includes several essential components:

i) Physical Examination: Checking for swollen lymph nodes, enlarged spleen, or liver.

ii) Blood and Urine Tests: Ruling out infections, identifying blood cell abnormalities.

iii) Serum Chemistry Tests: Assessing liver function and ruling out tumor lysis syndrome.

iv) Imaging: computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans to detect lymphoma spread.

v) Biopsy: Removing lymph node or bone marrow tissue for examination.

vi) Lumbar Puncture (spinal tap): If central nervous system involvement is suspected.

vii) Pathological Examination: Microscopic analysis of tissue to determine NHL type and characteristics.

viii) Immunophenotyping: Identifying markers on lymphoma cells.

ix) Additional Tests: Serum beta-2 microglobulin (β2M) and Human T-cell Lymphotropic Virus-1 (HTLV-1) serology in specific cases (McCarten et al., 2019; Sapkota & Shaikh, 2020).

1.9 Staging of Non-Hodgkin Lymphoma

To determine the extent of NHL, staging is essential. The current standard is the Lugano classification, an evolution of the Ann Arbor system with Cotswolds modifications (Munakata et al., 2019). It categorizes NHL based on tumor location and number of lymph nodes. Stage I involves a single lymph node region (stage I) or

a solitary extranodal site (stage IE). Stage II denotes multiple lymph nodes on the same side of the diaphragm (stage II) or localized extranodal disease (stage IIE). Stage III contains lymph node involvement on both sides of the diaphragm. Stage IV signifies widespread disease involving at least one extranodal organ (e.g., liver, bone marrow, lung) (Sapkota & Shaikh, 2020). The subscript "E" " is used to indicate limited extranodal extension, while more extensive involvement is classified as stage IV. Spleen is considered a nodal site in this system. Staging plays a crucial role in determining treatment options and predicting outcomes (Sapkota & Shaikh, 2020; Singh et al., 2020) (Table 1.1).

Table 1.1 Staging Non-Hodgkin Lymphoma: The Ann Arbor Classification with Cotswold Modifications

Stage	Defining status
Stage I	Restricted to a single lymph node region (I) or a single extranodal site (I-E).
Stage II	Two or more areas of nodal involvement on the same side of the diaphragm (stage II) or one or more lymph node regions with an extranodal site (II-E).
Stage III	Lymphatic involvement on both sides of the diaphragm (III), possibly with an extranodal site (III-E), the spleen* (III-S), or both (III-SE).
Stage IV	Liver, bone marrow, or other extensive extranodal disease.
Substage	
Substage E	Localized, extranodal disease.
Substage A	Absence of systemic signs.
Substage B	Presence of unexplained weight loss (10% in 6 months), and/or unexplained fever, and/or night sweat.

*The spleen is considered nodal

1.10 Classification and Prognostic Systems for Non-Hodgkin Lymphoma

NHL classification systems continue to evolve, reflecting advances in understanding and treatment. Prognosis varies significantly based on whether the lymphoma is slow-growing (indolent) or rapid-growing (aggressive). Indolent lymphomas have a more favorable prognosis, with untreated survival measured in

years, while aggressive lymphomas have an unfavorable prognosis, with untreated survival measured in weeks to months (Chisholm-Burns et al., 2022; Dipiro et al., 2020)

Prognostic factors for NHL include histologic subtype and clinical characteristics, including:

i) Age over 60 years.

ii) Poor performance status, assessed using scales like the eastern cooperative oncology group (ECOG) scale, which ranges from 0 to 5, with ECOG $\geq$ 2 indicating impaired functionality and a worse prognosis.

iii) Elevated lactate dehydrogenase (LDH) levels.

iv) Extranodal involvement.

v) Advanced disease (Stage III or IV) (Chisholm-Burns et al., 2022; Dipiro et al., 2020).

1.11 Treatment Considerations for Non-Hodgkin Lymphoma

The primary goals in treating NHL are to:

i) Cure the disease: Eradicate the NHL when possible, aiming for remission without relapse.

ii) Alleviate symptoms: Manage discomfort caused by the disease, such as swelling, fatigue, and pain, to improve quality of life.

iii) Minimise serious toxicities: Reduce side effects from chemotherapy and radiation, using supportive care to preserve overall health (Dipiro et al., 2020).

Treatment strategies for NHL depend on factors such as patient age, histologic type, disease stage and site, prognostic factors, patient preferences, and comorbidities. Based on these factors, treatment may involve observation, chemotherapy, radiotherapy, or a combination of chemotherapy and radiotherapy. Treatment is categorized also based on the extent of disease spread into limited disease (localized, Ann Arbor stages I and II) and advanced disease (Ann Arbor stages III and IV, or stage II with poor prognostic features) (Chisholm-Burns et al., 2022; Dipiro et al., 2020).

Options include radiation therapy (RT), often used to induce remission in early-stage disease and as palliative care in advanced stages; chemotherapy, ranging from single-agent therapy for indolent lymphomas to complex regimens for aggressive forms; and biologic agents. Follicular lymphomas, commonly found in older adults, usually present with advanced disease and chromosomal translocation t(14;18). Though these lymphomas generally have an indolent course and a median survival of 8-10 years, the natural history is unpredictable, with 20%-30% of patients experiencing spontaneous regression (Dipiro et al., 2020).

1.12 Pharmacotherapy of Non-Hodgkin's Lymphoma

The pharmacotherapy of NHL involves several types of medications and combinations depending on the specific subtype, stage, and other patient factors. Here are the primary types of pharmacotherapies used.

1.12.1 Chemotherapy

Chemotherapy is the mainstay of treatment modality for patients with NHL, especially those with advanced disease. Although malignant lymphoma has been

considered a fatal disease for several decades, recently it can be treated by introducing more effective chemotherapy regimens. For example, most NHL patients with aggressive stages have good responses with high cure rates to the intensive chemotherapy regimens (Chisholm-Burns et al., 2022). Furthermore, high-dose chemotherapy can be used as an intensive regimen and salvage therapy in autologous hematopoietic stem cell transplantation, contributing to increased recovery rates. Since chemotherapy-related toxicities, such as chemotherapy-induced nausea and vomiting, myelosuppression, infections, and mucositis are associated with such intensive chemotherapy regimens, it is important to provide NHL patients with the appropriate supportive care therapy in a timely manner (Dipiro et al., 2020; Lin et al., 2018).

The most effective chemotherapy agents associated with higher cure rates include cyclophosphamide, bleomycin, doxorubicin, purine analogues, etoposide, methotrexate, vincristine, and corticosteroids. Typically, the most common regimen for NHL includes several cycles of CHOP/R-CHOP administered every 3 weeks, which include rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. Clinical evidence has shown that the rituximab-based regimen is associated with longer overall survival. Additionally, the most common chemotherapy agents used as salvage regimens include ICE (ifosfamide, carboplatin, and etoposide), DHAP (dexamethasone, high-dose cytarabine (Ara-C), and cisplatin), and ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) (Chisholm-Burns et al., 2022; Dipiro et al., 2020).

1.12.2 Radiation therapy

Since NHL is more often a systemic disease, radiation therapy plays a more limited role compared to Hodgkin Lymphoma (HL). It is primarily used in advanced cases, mainly as a palliative measure to control localized bulky disease or as consolidation therapy after chemotherapy, especially in patients with large extranodal masses. Radiation therapy employs high-energy beams, such as X-rays and protons, to destroy cancer cells. During treatment, a large machine directs these beams to precise points on the body. For some NHL types, especially if the lymphoma is slow-growing and confined to one or two areas, radiation may be the sole treatment required. More commonly, it is used after chemotherapy to target residual lymphoma cells and affected lymph nodes, as well as nearby areas where the disease might spread (Chisholm-Burns et al., 2022; Dipiro et al., 2020).

1.12.3 Immunotherapy and Monoclonal antibodies

Immunotherapy uses the body's immune system to fight cancer. Cancer cells can evade detection by producing proteins that help them hide from immune cells. Immunotherapy with monoclonal antibodies targets these proteins, helping the immune system recognize and attack cancer cells. This approach may be considered for certain types of NHL, particularly if other treatments have been ineffective. Monoclonal antibodies target the CD20 protein found on the surface of B cells, which are often involved in NHL. It is frequently used in combination with chemotherapy or other agents and can improve treatment outcomes, such as rituximab or newer agents like obinutuzumab and ofatumumab may be used (Chisholm-Burns et al., 2022; Dipiro et al., 2020).

1.12.4 Targeted drug therapy

Targeted drug therapy focuses on specific abnormalities in cancer cells, blocking these abnormalities to induce cell death. For NHL, targeted drugs can be used alone or in combination with chemotherapy. Medications such as ibrutinib, idelalisib, and venetoclax are increasingly utilised, especially for certain NHL subtypes. This approach can be employed both as initial treatment and as a subsequent option if the lymphoma recurs (Makita et al., 2020, Chisholm-Burns et al., 2022)

1.12.5 Engineering immune cells to fight lymphoma

Chimeric antigen receptor-T-cell (CAR-T) therapy is a specialized treatment that involves extracting T cells from a patient, modifying them to target cancer cells, and then reintroducing them into the body. CAR-T therapy may be an option for certain types of B-cell NHL that is refractory or relapsed, and unresponsive to other treatments (Yin et al., 2021).

1.12.6 Bone marrow transplant

A bone marrow transplant, also called a stem cell transplant, involves administrating high doses of chemotherapy and radiation to suppress the bone marrow and immune system. Healthy stem cells from the bone marrow, either from the patient or a donor, are then infused into the bloodstream, where they travel to the bones and rebuild the bone marrow. This treatment are key treatments for relapsed/refractory DLBCL and may be considered for NHL patients if other therapies have been ineffective (Dipiro et al., 2020, Berning et al., 2024).

1.13 Treatment Outcomes in Non-Hodgkin's Lymphoma

Treatment outcomes in NHL are broadly classified based on clinical, imaging, and patient-reported parameters to guide treatment decisions and predict prognosis. Optimal therapy in NHL reflects favorable outcomes, signifying effective disease control with minimal toxicity, tailored to the NHL subtype, stage, and patient-specific factors. In contrast, unfavorable outcomes indicate disease progression, relapse, refractory disease, or significant treatment-related morbidity (Cheson et al., 2014, Tilly et al., 2015). Key parameters for measuring outcomes in NHL include:

i) Progression-Free Survival (PFS): Duration without disease progression during or after treatment.

ii) Overall Survival (OS): Time from treatment initiation to death from any cause.

iii) Response Rates (RR): Proportion of patients achieving complete response (CR) or Partial Response (PR), often assessed via PET-CT.

iv) Quality of Life (QOL): Evaluation of physical, emotional, and functional well-being using validated tools. These parameters help assess therapeutic effectiveness and support evidence-based strategies for optimizing patient outcomes (Zelenetz et al., 2023).

1.14 Physicians' and Nurses' Knowledge and Practice Regarding Pharmacotherapy of Non-Hodgkin's Lymphoma

Healthcare providers, including physicians and nurses, play a crucial role in the effective implementation of cancer control measures, particularly in early case identification and management. However, inadequate knowledge of cancer

pharmacotherapy among healthcare providers can negatively impact their clinical practice, attitudes, and beliefs, leading to suboptimal patient outcomes (Mubin et al., 2021). Knowledge gaps in clinical guidelines and pharmacotherapy contribute to suboptimal cancer care, increasing the risk of mismanagement, delayed treatment, and adverse drug reactions. These deficiencies often lead to inconsistent adherence to treatment protocols, impacting patients' quality of life and treatment outcomes (Mubin et al., 2021). This is further exacerbated in resource-limited settings like Yemen, where healthcare providers may lack access to updated training and resources, hindering the implementation of evidence-based treatment practices.

Evaluating healthcare professionals' knowledge and practices in the management of NHL is essential for identifying gaps and improving adherence to clinical guidelines. Such an assessment offers valuable insights into the influence of current practices on patient care and supports the development of targeted strategies to optimise treatment outcomes. Adhering to pharmacotherapy guidelines is critical, as non-compliance frequently leads to suboptimal care and diminished patient outcomes (Stienen et al., 2015). Strengthening the knowledge and practices of healthcare providers is essential for optimizing pharmacotherapy, improving treatment success, and enhancing patient care in resource-constrained environments.

In particular, nurses who administer chemotherapy must have proper qualifications and training to ensure safety. Continuous education in oncology nursing is essential for improving their knowledge and adherence to safety protocols, which directly contributes to better patient outcomes (Hosen et al., 2019). Furthermore, nurses with expertise in managing chemotherapy-induced peripheral neuropathy play a vital role in improving patients' quality of life (Al-Atiyyat & Banifawaz, 2018).

Nurse-led education is also crucial for high-quality cancer care. Nurses are pivotal in educating patients, answering their questions during treatment, and offering support. Patients frequently seek guidance on adjusting their daily routines to enhance well-being and safety during chemotherapy (Rogers et al., 2021).

1.15 Drugs-Related Problems of Non-Hodgkin's Lymphoma Pharmacotherapy

Drug-related problems (DRPs) are a significant concern in healthcare, particularly for patients with complex conditions like NHL. DRPs are defined by the Pharmaceutical Care Network Europe (PCNE) as “events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes” (Silva et al., 2015).

The World Health Organization estimates that over 50% of all prescribed medications are associated with DRPs (Su et al., 2021). DRPs can lead to significant harm in both hospital and outpatient settings, including illness and death. These problems arise from factors such as incorrect dosages, adverse reactions, ineffective treatments, and non-compliance (Bekele et al., 2021). Globally, 10% to 20% of inpatients experience adverse reactions during their hospital stay, with 5% to 10% of hospital admissions attributed to DRP, more than half of which are preventable (Coleman & Pontefract, 2016; Niriayo et al., 2018). DRPs can decrease patients' quality of life, prolong hospital stays, increase healthcare costs, and lead to readmissions, impacting both patients and healthcare providers (Bekele et al., 2021).

In cancer care, chemotherapy's varying toxicity levels can exacerbate DRPs, affecting treatment outcomes and patients' quality of life (Wang et al, 2015; Farha et al., 2017). The increasing complexity of chemotherapy regimens and the rise in drug

use contribute to a higher incidence of DRPs, including adverse drug reactions (ADRs), drug-drug interactions (DDIs), unnecessary drug therapy, inappropriate drug choices, untreated conditions, and the need for additional medications to manage side effects (Sisay et al., 2015; Leendertse et al., 2008). DRPs can be complex, with a single medication potentially causing multiple issues, and patients may experience only one symptom despite several underlying problems (Ruths et al., 2007).

In patients with NHL, factors such as malnutrition, reduced serum-binding proteins, edema, or hepatic/renal dysfunction can alter pharmacokinetic parameters, increasing the risk of DRPs. Moreover, the complexity of chemotherapy for patients with NHL further underscores the importance of comprehensive pharmaceutical care. Therefore, healthcare providers, including clinical pharmacists, should prioritize minimizing treatment-associated risks in these patients (Sisay et al., 2015; Kefale et al., 2022).

1.16 Chemotherapy-Induced Nausea and Vomiting of Non-Hodgkin's Lymphoma

Despite advances in antiemetic therapies, chemotherapy-induced nausea and vomiting (CINV) remains a troublesome issue affecting 70-80% of adult cancer patients undergoing chemotherapy (Hesketh et al., 2017). These distressing complications not only cause physical discomfort, but also lead to various negative consequences, including metabolic dysfunction, nutritional depletion, appetite loss, potential esophageal damage, premature termination of treatment, deterioration of self-care and functional capacity**,** and impact patients' quality of life and treatment adherence (Piechotta et al. 2021; Hesketh et al., 2017).

Emetogenic potential in chemotherapy refers to the likelihood of a regimen causing nausea and vomiting. Chemotherapy regimens are classified based on the emesis potential classification (EPC) to guide appropriate antiemetic prophylaxis into highly emetogenic chemotherapy (HEC), with over a 90% chance of inducing emesis, moderately emetogenic chemotherapy (MEC), with a 30-90% chance of inducing emesis, low emetogenic chemotherapy (LEC), and minimal emetogenic chemotherapy, with less than a 30% likelihood of emesis (Hesketh et al., 2017; Wakasugi et al., 2019). According to the NCCN guidelines, there are three options (A, B, and C) for antiemetic prophylaxis for HEC. Option A includes olanzapine or NK1-RA, option B excludes NK1-RA but includes olanzapine, and option C excludes olanzapine but includes NK1-RA (Table 1.2).

Table 1.2 CINV prophylaxis recommendations for IV chemotherapy

EPC	Phase	NCCN
HEC	Acute phase	Option A (preferred): olanzapine + NK1-RA + 5-HT3-RA + dexamethasone Option B: olanzapine + palonosetron + dexamethasone Option C: NK1-RA + Any 5-HT3-RA + dexamethasone
MEC	Acute phase	Option D: 5-HT3-RA + dexamethasone Option E: Olanzapine + palonosetron + dexamethasone Option F: NK1-RA + 5-HT3-RA + dexamethasone
LEC	Acute phase	Dexamethasone or metoclopramide or prochlorperazine or 5-HT3-RA
Minimal	Acute phase	No routine prophylaxis

Abbreviations: EPC, emetogenic potential risk chemotherapy; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; LEC, low emetogenic chemotherapy; NK1: neurokinin1 receptor antagonists; 5HT3-RA, 5-hydroxytryptamine-3 receptor antagonist. NCCN: National Comprehensive Cancer Network.

Chemotherapy regimens for NHL vary in emetogenic potential, classified by the EPC. CHOP and R-CHOP regimens that are commonly used for both B-cell and T-cell NHL are classified as MEC per CINV guidelines at standard doses (Takahashi

et al., 2016, NCCN 2022). Other MEC regimens include R/CVP, DA-EPOCH/R, Hyper CVAD/R, and ESHAP/R. High emetic risk (HEC) regimens include high-dose cyclophosphamide (>1500 mg/m²), high-dose doxorubicin (≥60 mg/m²), DHAP/R, and dose-modified CODOX-M. Low to minimal emetic risk regimens, typically involve Rituximab (NCCN, 2022). Recognizing the emetogenic potential of these regimens is essential for tailoring antiemetic prophylaxis, ensuring patient comfort, and maintaining treatment adherence.

Although anthracycline- and cyclophosphamide-based regimens are known to induce CINV, the use of neurokinin-1 (NK1) receptor antagonists for CINV prophylaxis in aggressive NHL is uncertain, particularly in the context of the standard CHOP and R-CHOP regimens. This uncertainty arises from the inclusion of prednisone in these regimens as prednisone has been shown to lower the risk of CINV (Tamura et al. 2015, Wakasugi et al., 2019). Therefore, NK1 receptor antagonists are often not routinely administered to patients receiving CHOP or R-CHOP therapy for CINV prophylaxis in clinical practice. Prophylactic regimens of CINV are recommended based on the emetogenicity risk potential of the chemotherapy regimen, with triple antiemetic prophylaxis for highly emetogenic regimens being the standard (Molassiotis et al., 2017).

Despite guidelines recommending antiemetic prophylaxis for controlling CINV, adherence remains suboptimal, particularly for patients undergoing highly emetogenic multi-day chemotherapy, partly due to a lack of awareness of recent guideline updates (Uchida et al., 2022), as these guidelines updates recomended adding olanzapine and/or NK1 receptor antagonists (e.g., aprepitant) to prophylactic regimens alongside 5-HT3 receptor antagonists and dexamethasone for HEC, improving control of both acute and delayed CINV phases (NCCN, 2022).

Additionally, clinical outcomes often fall short, and CINV remains a persistent complication in cancer treatment (Vazin et al., 2017). The implementation of evidence-based antiemetic regimens, as outlined by international and national guidelines, plays a crucial role in effectively managing CINV in cancer patients (Aapro et al., 2021). On the other hand, deviation from these guidelines can lead to suboptimal CINV control, highlighting the importance of consistent adherence to established protocols (Aapro et al., 2021).

1.17 Health-Related Quality of Life of Non-Hodgkin's Lymphoma

NHL pharmacotherapy significantly impacts patients' health-related quality of life (HRQOL). HRQOL reflects an individual's self-perceived well-being influenced by disease and treatment (Webster et al., 2005). NHL-related impairments, including treatment toxicities and the disease itself, affect physical, psychological, and social well-being (Kang et al., 2018; Kim et al., 2014). Factors such as age, disease stage, and treatment intensity influence HRQOL outcomes (Amatya et al., 2023).

NHL patients experience various HRQOL challenges. Advanced-stage patients and treatment-related side effects, including neuropathy, fatigue, and cardiotoxicity, impair physical functioning and psychological well-being. The diagnosis itself can also be psychologically distressing for patients and their families (Mols et al., 2007; Smith et al., 2009; Joshy et al., 2020). During recovery period, NHL patients may encounter increased care needs, work and driving limitations, financial strain, fear of recurrence, and reduced social participation (Amatya et al., 2023; Oerlemans et al., 2014). Moreover, long-term survivors also struggle with persistent physical limitations, financial strain, and social isolation. These issues

collectively impact activity, participation, and overall quality of life (Tsatsou et al., 2021; Sitlinger & Zafar, 2018).

Measuring HRQOL is essential for understanding patients' experiences and evaluating treatment effectiveness. Several tools are available for evaluating HRQOL in NHL patients, including the functional assessment of cancer therapy-lymphoma (FACT-Lym), European organisation for research and treatment of cancer core quality of life questionnaire (EORTC QLQ-C30) and EuroQol five dimensions-5 level (EQ-5D-5L). Among these, FACT-Lym is the most detailed and lymphoma-specific, making it particularly relevant for NHL patients. The EORTC QLQ-C30 is a general cancer tool adaptable for NHL, but less sensitive to lymphoma-specific issues. The EQ-5D-5L is quick and widely used but lacks lymphoma-specific details and is mainly for broad HRQoL and economic assessments (Shah et al., 2021; Wasse et al., 2023).

FACT-Lym evaluates HRQOL across physical, social/family, emotional, and functional well-being domains, addressing patient concerns related to symptoms, complications, and treatment. The total score ranges from 0 to 168, providing a comprehensive assessment of lymphoma-specific QOL (Webster et al., 2005; Shah et al., 2021).

Addressing the HRQOL needs of NHL patients is crucial. While cure remains a primary goal, improving patients' quality of life is equally important. The FDA's inclusion of HRQOL as a primary outcome in NHL trials underscores its significance (Quinten et al., 2009). Further research is needed to understand the impact of DRPs on HRQOL in this population (Sisay et al., 2015; Farha et al., 2017).

1.18 Statistics and Pharmacotherapy of NHL in Yemen

Yemen, as reported by WHO: Globocan (2020), has experienced an increasing prevalence of cancer. In 2020, there were a total of 16,476 new cancer cases, with 7,159 cases among males and 9,317 cases among females. The age-standardised incidence rate per 100,000 was 92.7 for males, 102.2 for females, and 97.0 for both sexes. The risk of developing cancer before the age of 75 was 9.3% for males, 10.3% for females, and 9.8% for both sexes. The number of cancer deaths in Yemen in 2020 reached 12,103. The age-standardised mortality rate per 100,000 was 77.9 for males, 76.1 for females, and 76.5 for both sexes. The 5-year prevalence of cancer cases was 26,651 (WHO: Globocan, 2020). Moreover, NHL was one of the most frequent cancers in Yemen. It accounted for 862 new cases in Yemen, ranking 5th in terms of the number of cases among both sexes, and ranking 3rd among males. Breast cancer was the most common cancer among both males and females, accounting for 17.6% of new cases, followed by colorectal cancer at 9.2%, leukemia (6%), and stomach cancer (5.9%). Among males, colorectal cancer was the most common (11%), followed by stomach cancer (7.6%) (WHO: Globocan, 2020). It represented 5.2% of all new cancer cases, with a cumulative risk of 0.41%. The number of deaths due to NHL was 591, ranking 9th in terms of mortality, with a cumulative risk of 4.9%. The 5-year prevalence of NHL cases was 1,510, representing 5.06% of all prevalent cancer cases (WHO: Globocan, 2020), see Figure 1.3. However, Globocan, 2022 report in the Yemeni context showed small differences compared to the Globocan 2020 data. In 2022, NHL accounted for 851 new cases in Yemen, ranking 6th in terms of the incidence among both sexes and 3rd among males. It represented 5.2% of all new cancer cases with a cumulative risk of 0.35%. The number of deaths due to NHL was 585 cases representing 4.9%, ranking as the 9th

highest number of deaths, with a cumulative risk of 0.25. The 5-year prevalence of NHL cases was 1,829 cases representing 5.8% of all prevalent cancer cases (Figure 1.4) (WHO: Globocan, 2022). In Aden governorate, NHL was the most prevalent hematological malignancy in 2010. Additionally, in 2013, lymphoma accounted for 9.8% of all cancer patients attending the National Oncology Center (NOC), with NHL comprising 65% of all lymphoma cases (Aldaeri et al., 2022; Ebrahim & Albishi, 2021). These statistics emphasise the need for effective prevention, early diagnosis, and appropriate treatment strategies for this disease.

Yemen has five registered functioning Oncology Centers: ؜؜National Oncology Center (NOC) in Sana'a, NOC in Aden, NOC in Hadramout Al-Mukalla, and NOC in Hadramout Valley and Desert (Seiyun), and Al-Amal Oncology Center in Taiz. Additionally, two new oncology centers have recently opened in Shabwa and Marib (Hamid & Noman, 2022). These centers face numerous challenges, including limited healthcare services, transient populations, financial constraints, lack of qualified personnel, incomplete data coverage, and difficulties in establishing reliable registries and obtaining cancer mortality data (Bawazir et al., 2022). In Yemen, oncology centers are specialized facilities offering comprehensive cancer care, including advanced diagnostics and treatments, while oncology units are departments within general hospitals providing basic cancer treatment, often referring patients for specialized care. Oncology centers are more equipped and focused on cancer, whereas oncology units operate within broader hospital settings (Hamid & Noman, 2022).

The National Cancer Control Program (NCCP) in Yemen, operates public centers across different cities, including Sana'a, Aden, Hudaidah, Taiz, Mukalla, Seiyun, and Ibb, where almost all chemotherapy medications are provided free of