CONSENSUS DOCUMENT FOR MANAGEMENT OF NON HODGKIN'S LYMPHOMA (HIGH GRADE)

Prepared as an outcome of ICMR Subcommittee on Non Hodgkin's Lymphoma (High Grade)

Coordinated by

Division of Non Communicable Diseases

Indian Council of Medical Research
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Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

Dr. Soumya Swaminathan
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for consensus document for management of non- hodgkin's lymphoma- high grade. The ICMR had constituted sub-committees to prepare consensus document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.

This consensus document on management of non- hodgkin's lymphoma – high grade summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in formulating site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. Hope that this document would provide guidance to practicing doctors and researchers for the management of patients suffering from non- hodgkin's lymphoma – high grade and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on subject based on available evidence. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of Consensus Document on Management of non- Hodgkin's lymphoma – high grade would serve the desired purpose.

(Dr. S Swaminathan)
Secretary, Department of Health Research
& Director-General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer.

The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and Pediatric Lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2012 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall; worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2009-2011) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface

Lymphoma is a type of cancer that develops in the lymphatic system, the body's disease fighting network. It is estimated that around 1,000 people worldwide are diagnosed with lymphoma every day. Globally the incidence of disease is 385741 cases with mortality of 199650 cases. India accounts for 23801 cases with a mortality of 16597 cases.

Lymphomas are a very complex group of diseases with differing behaviours and treatment options. It is typically classified into two groups, Hodgkins lymphoma (HL) and non-Hodgkins lymphoma (NHL). NHL'S are subclassfied as low grade (indolent) and high grade. The high grade NHL is generally curable with cytotoxic therapy while the low grade lymphomas are controllable for long periods. While lymphoma is potentially fatal, some forms are curable and a patient's survival may be greatly enhanced by early diagnosis. Almost all lymphoma types can be cured or managed as a chronic disease, but its complexity and variation do not allow for a one-size-fits-all treatment approach. Instead, it necessitates highly specialized and individualized approaches .The cause of the majority of lymphoma cases is unknown, however, there could be several factors that may influence one's risk of developing lymphoma. The relative effects of these factors in any given case of cancer vary and are very difficult to determine with accuracy at present.

The purpose of this work was to revamp recommendations for evaluation, staging and response assessment of patients with non-Hodgkin's lymphoma. The availability of more effective therapies for lymphoma and the increasingly sensitive and specific technologies has made this consensus the need of hour. However, good clinical judgement, a careful history and physical examination are the cornerstones of patient follow up. The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with Non Hodgkin Lymphoma – High Grade (NHL-HG). The guidance may not be appropriate for all patients with NHL but this compilation of Indian Data gives us an insight to best practice. This disease strata is currently undergoing extensive investigations and it is likely that paradigms will shift over the next several years, To accommodate these likely changes, the guidelines will require modification to keep apace with new developments.

I take this opportunity to acknowledge and thank the entire task force committed to the compilation of the consensus document. I would also like extend my gratitude to Dr. G.K.Rath whose vision and unstinted support inspired us for this contribution. I would like to thank all authors and reviewers for having taken time from their busy schedules to help us. I do hope that the work done will stimulate further research and enable evidence based policy formulation. If that is indeed done, the efforts put in will not go in vain and the mission would be accomplished.

(Dr. D.C. Doval)
Chairperson
Subcommittee on NHL-HG

Preface

Cancer is a leading cause of death worldwide. Globally Cancer of various types affects millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

Dr Bela Shah
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.

This document represents a joint effort of large effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Soumya Swaminathan, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking her special interest and understanding the need of formulating the guidelines which are expected to benefit clinicians & cancer patients.

I would like to acknowledge here the initiative undertaken with the able guidance of Dr. Bela Shah. I would like to thank Dr. DK Shukla for his support and coordination in finalizing this document. I would like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

Tanvir Kaur

(Dr. Tanvir Kaur)
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CHAPTER 1

INTRODUCTION

Lymphomas are a heterogenous group of lymphoproliferative disorders originating in B-, T-, or natural killer (NK) lymphocytes. In India, B-cell lymphomas represent 80 to 85% of all cases, T-cell approximately 15 to 20% and NK cell are rare.

The incidence of lymphomas worldwide has increased between 1970 -1995. This increase has been attributed to the Human immunodeficiency virus (HIV) epidemic and the development of Acquired immune deficiency syndrome (AIDS) related Non Hodgkin lymphoma (NHL). The increased incidence has been observed in patients in their sixth and seventh decade. It has paralleled a decline in mortality due to other causes. In India too the incidence of lymphomas has shown an increase in the last decade.

Broadly, lymphomas comprise of Hodgkin's lymphoma (HL) and NHL. NHL's are subclassified as low grade (indolent) and high grade. The high grade NHLs are generally curable with cytotoxic chemotherapy while the low grade lymphomas are controllable for long periods. Hence, it is not only important to make the correct diagnosis of the lymphoma but also essential to subclassify them correctly to high grade NHL or low grade NHL in order to give appropriate treatment.

1.1 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues[1]

MATURE B-CELL NEOPLASMS

- Chronic lymphocytic leukemia / small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic B-cell marginal zone lymphoma
- Hairy cell leukemia
- Splenic B-cell lymphoma/leukemia, unclassifiable
    - *Splenic diffuse red pulp small B-cell lymphoma*
    - *Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
    - Waldenström macroglobulinemia
- Heavy chain diseases
    - Alpha heavy chain disease
    - Gamma heavy chain disease
    - Mu heavy chain disease

- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
    - *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
    - *Pediatric follicular lymphoma*
- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
    - T-cell/histiocyte rich large B-cell lymphoma
    - Primary DLBCL of the CNS
    - Primary cutaneous DLBCL, leg type
    - *EBV positive DLBCL of elderly*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

MATURE T-CELL AND NK-CELL NEOPLASMS

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK cell leukemia
- Systemic EBV positive T-cell lymphoproliferative disease of childhood

- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NG/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
    - Lymphomatoid papulosis
    - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative

HODGKIN LYMPHOMA

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Intermediate dendritic cell tumor

- Disseminated juvenile xanthogranuloma

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

- Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)#
- Classical Hodgkin lymphoma type PTLD#

NOS- not otherwise specified.
The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.
#, these lesions are classified according to the leukemia or lymphoma to which they correspond.

1.2 Distribution of Lymphoma - Histology/ Age-Group

Common lymphoma subtypes in adults include[1,2]

1. Diffuse large B-cell lymphoma,
2. Hodgkin lymphoma,
3. Follicular lymphoma,
4. T-cell lymphoblastic lymphoma,
5. Small lymphocytic lymphoma,
6. Burkitt's lymphoma,
7. Anaplastic large cell lymphoma etc.

Common lymphoma subtypes in children[1,3]

1. T lymphoblastic lymphoma,
2. Hodgkin lymphoma,
3. Burkitt's lymphoma,
4. DLBCL,
5. Anaplastic large cell lymphoma.

CHAPTER

2 DIAGNOSIS

Accurate diagnosis in Hematolymphoid neoplasm (HLN) requires a combination of detailed history, clinical examination, and various investigations including routine laboratory tests (complete blood counts, liver and renal function tests, Lactate dehydrogenase (LDH), uric acid, beta-2 microglobulin, Erthyocyte sedimentation rate (ESR), peripheral blood smear), good quality histology section (of tumor and also bone marrow aspirate/biopsy), immunostaining, cytogenetic and molecular studies and radiology investigations (X-Ray chest, abdominal Ultrasound (USG), Computed tomography (CT) abdomen/thorax and/or Positron Emission Tomography- Computed Tomography (PET-CT). Diagnostic workup includes testing for various viral markers including Human immunodeficiency virus (HIV), Hepatitis C virus (HCV) and Hepatitis B Virus (HBV).

The organization of a hematopathology laboratory may vary from a large size hematopathology laboratory capable of performing all tests in-house (institute based or a private reference laboratory) to a small size laboratory doing only preliminary tests such as morphology on Hematoxylin & Eosin (H&E) stained sections. These laboratories may send samples / paraffin block to reference laboratories for specialized tests like Immunohistochemistry (IHC)/ Flow Cytometry (FCM), cytogenetics and molecular genetics services.

As HLN occurs at extranodal sites, they get reported by other specialists like pediatric, gastrointestinal, skin or neuro pathologists. It is recommended that these specialists have access to an expert haematopathology opinion. Pathologists are recommended to obtain a second opinion on all doubtful cases from an expert hematopathologist. This may help in preventing repeat biopsies, reduces the turn around time and also reduce the chance of misdiagnosis.

There is no single gold standard for lymphoma diagnosis. Good quality H&E section is the mainstay for the diagnosis of lymphomas. Microscope shall have a scanner lens 1X or 2X. Other lenses may be 4X, 10X, 20X, 40X and 100X (oil immersion). Standard protocols should be followed for processing of tissues.

2.1 Indication for biopsy

In adults, under normal conditions, only the inguinal nodes are palpable as 0.5-2.0cm nodules. However, any lymphadenopathy (solitary or generalized), size >1.5cm, long standing (4-6 weeks), firm, movable, non tender, hard and suggestive of lymphoma must be biopsied. It is advisable to do a whole node biopsy of the largest palpable node. Other indications may include persistent lymphadenopathy, mediastinal mass, abdominal mass or any other extranodal mass and unexplained fever. History of persistent B symptoms, hepatosplenomegaly indicate need of a biopsy of any palpable mass.

Morphological asessment is the first step in the diagnosis of NHL. However, before invasive procedures are attempted, a complete blood count with a manual differential count should be done as the presence of cytopenia or increased leukocyte counts may suggest a bone marrow involvement. In

such cases, peripheral blood smear with Immunophenotyping (IPT) by FCM can be done for diagnosis, thereby obviating need of invasive tests and risks of anesthesia. In patients who present with acute severe respiratory distress due to airway obstruction (superior vena cava syndrome due to a mediastinal mass), every attempt should be made to make a diagnosis before starting steroids or chemotherapy as otherwise it may jeopardize the diagnosis. A diagnostic tap of pleural fluid or ascites may reveal tumor cells in T-lymphoblastic and Burkitt's lymphoma respectively. Laprotomy and resection of the bowel may be indicated in patients who present with intussusception or intestinal obstruction.

Few patients referred to a tertiary care center for further management have already received preliminary treatment in form of blood transfusion or steroids. This might cause a temporary decrease in tumor load leading to a delayed diagnosis. In such situations, a trephine if done upfront at the primary center is extremely helpful, as this material can be used to perform IHC on the paraffin block to further subtype. Such paraffin blocks are invaluable material as IHC can be performed at later stage even if there are no blasts seen on peripheral blood or repeat bone marrow (BM) aspirate.

2.2 Procedure, collection and transport of specimen

Consent for all laboratory procedures as well as investigations essential for diagnosis, including Deoxy ribonucleic acid (DNA) analysis, should be part of the initial consultation with the patient.

In all cases, adequate clinical information is essential to assess the risk of the disease and plan the investigations. Request forms must include relevant clinical as well as laboratory information including complete blood counts, biochemical investigations and results of any preceding investigations such as peripheral blood IPT.

Lymph nodes (LN): The LN biopsy should be done by a surgeon, endoscopic biopsy by a gastroenterologist, and skin biopsy by a dermatologist. Whole node biopsy of the largest palpable node should be done. Multiple cores may be obtained from the deep seated lesions such as abdominal, mediastinal and retroperitoneal nodes. Needle core biopsy may be done for non palpable lesions. The use of blunted needles, forceps is not recommended so as to avoid crushing of nodal tissue.

If LN biopsy cannot be transported to the histopathology laboratory immediately, LN should be sliced serially perpendicular to its long axis and fixed in optimum quantity of buffered formalin (10 times volume of the biopsy). It will ensure optimum preservation of morphology and good results on IHC.

Specimens preferably the entire node should reach the laboratory immediately after collection since cytogenetic analysis requires live cells for culture and RNA degrades rapidly. When a specialized test like FCM or cytogenetic analysis is to be carried out at a remote location, transport in appropriate tissue culture media should be done.

Frozen section should be avoided if lymphoma is suspected as freezing cause artifacts and also loss in tissue during processing (to be discussed in detail with surgical colleagues). A part of sample may be sent for snap frozen for preservation of sample for ancillary molecular investigations.

Tissue Grossing and Fixation: Mention the number of the nodes and size of the largest node. The LN may be sectioned into multiple slices (3-4 mm) perpendicular to the long axis of the node. This orientation provides the greatest assessment of the architecture. Majority of the tissue is put in formalin for histopathology laboratory. Grossing may be done on fresh LN tissue by the surgeon in the operation theatre (OT) itself. The bisected LN tissue should be fixed in formalin for 24-48 hours; less than this might lead to poor preservation of cytological detail and can make the tissue uninterpretable. Standardization of fixation makes IHC more reliable. Prolonged fixation makes IHC more difficult and recovery of DNA from paraffin blocks unreliable.

Bone marrow: BM aspirate and biopsy shall be done by an experienced physician / pathologist. BM biopsy is a painful procedure and should be done under adequate local anesthesia. Trephine core of at least 1.6 cm length should be obtained. Bone marrow aspirate smears should be prepared immediately, using wedge slide method (similar to peripheral blood smear preparation). Imprint smears should be prepared by rolling of trephine biopsy core on glass slides. Trephine biopsy should be immediately transferred to appropriate fixative.

Specimen handling in the laboratory: All biopsy samples are considered a potential biohazard. Proper handling of the specimen (including receiving, labeling etc) on its arrival in the laboratory is crucial to successful sample reporting. Record the size, colour and consistency and presence or absence of any visible nodularity, haemorrhage, or necrosis on the cut slices.

Imprints on glass slide may be made before transferring the node to formalin. These slides may be air dried (30 minutes) and transported as such to the laboratory. The pathologist may receive LN biopsies fresh, intact, or fixed in formalin. It is recommended that each laboratory establish a protocol for the handling of LN biopsies that ensures both optimal histological sections and preservation of material for ancillary studies. Tissue may be collected upfront in different fixatives for ancillary studies including DNA/ RNA and flow cytometry.

Extranodal biopsies and spleen: Fixation, grossing and tissue processing are extremely important so as to avoid autolysis of spleen. Measure the weight and describe the gross appearance including presence of any focal lesions (e.g., infarcts, nodules, hemorrhage), and gross abnormalities of red or white pulp. The spleen must be sectioned at 3-5mm intervals, to look for grossly identifiable lesions. Fixation, grossing and tissue processing are extremely important so as to avoid autolysis of spleen. Splenic Fine Needle Aspiration Cytology (FNAC) is not used as a diagnostic test. Biopsy from other sites like skin, gastrointestinal tract (GIT) are immediately transferred into formalin.

Note: In small LN and in needle core biopsies there may be material just enough for histopathology processing and no additional investigations may be possible. However, if the specimen received is a whole fresh LN, which has sufficient volume, the specimen can be divided. Major chunk of the tissue specimen is sent for histological sections (in formalin or other fixative) and a part may be divided for DNA/RNA or FCM studies.

2.3 Different samples and Ancillary techniques

Diagnostic modalities include morphology, cytochemistry (e.g., tartarate resistant acid phosphatase), IHC, FCM, cytogenetics (both conventional cytogenetics and Fluoroscent in-situ hybridization (FISH), and molecular diagnostics. These could be applied to different tissue samples as follows:

1. ***Peripheral blood and bone marrow aspirate specimens***

Apart from morphology, it is used for cytochemistry, FCM, PCR, FISH and conventional cytogenetic studies. It should be collected in evacuated tubes containing the appropriate anticoagulant (EDTA etc). Samples are best studied within 24 hours of collection. Heparin is preferred if a delay is anticipated (upto 72 hours) but this sample cannot be used for molecular evaluation.

Morphology: Staining by a Romanowsky stain.

Flow Cytometry: Samples for analysis by FCM should be kept at room temperature and received within 24 hours, as there can be sample degeneration or a reduction in antigen strength or complete loss of antigen with time.

Cytogenetics: Heparin is the preferred anticoagulant for peripheral blood and bone marrow. All blood samples should be rotated thoroughly to ensure adequate mixing with the anticoagulant or preservative and transported at room temperature.

Unfixed blood films made using silane-coated slides for FISH can be used. Such films must be made fresh, but can give adequate results even after years, stored at room temperature. They have an advantage that morphology can be seen alongside the FISH.

Molecular Tests: EDTA may be used as an anticoagulant for molecular tests such as RT-PCR. A sample of fresh tissue may be rapidly frozen and stored for subsequent analysis if required, such as DNA analysis.

As for peripheral blood, BM films are a highly acceptable alternative to cytogenetically prepared material if FISH testing is required. A negative result may be due to absence of the relevant cells from the sample (diluted sample) rather than absence of the abnormality from the tumor cells.

2. Lymph node and extranodal tissues

Major indication of a LN biopsy is for diagnosis and subtyping of the HLN. Largest palpable node is biopsied, or else adequate needle core biopsies are obtained, if lesion is not easily accessible.

Collection & preparation: Good quality thin section (<3 micron thick) stained with H&E stain is the mainstay. Lab shall follow standard published protocols for processing of LN biopsies.

Morphology: LN (and extranodal) biopsy sections should always be stained with H&E stain. Scanner view is most important followed by low power examination. Abnormal patterns, infiltrates and then cytological interpretation is done and described.

IHC is required in almost all suspected cases of HLN for diagnosis and further subtyping. Cases like classical HL may be diagnosed based on morphology, however, IHC is required in tricky cases to exclude close morphological differentials of NHL subtypes. This may be done by manual or automated methods.

For FCM, fresh LN samples are best analyzed as early as possible, preferably within 6-8 hours. If sample has to be transported to outside reference laboratory, lab shall have Standard operating procedures (SOPs) for disaggregating and fixation of the sample in a transport media.

For Cytogenetics, a fresh sample of the specimen in tissue culture medium should be sent for cytogenetic analysis. Cytogenetic analysis may be performed once the morphological impression is made. This may help in saving costs in unnecessary screening. FISH may be done on imprint smears as well as on tissue sections. If fresh samples are processed for metaphases, these should be stored. Analysis is attempted after morphological assessment of the sample indicates a need for cytogenetics. The cytogenetics laboratory may store cell suspensions.

3. Bone Marrow Trephine Biopsy

The major indication of trephine in lymphomas is for staging purposes. The trephine biopsy core should preferably be taken from the posterior superior iliac crest and should be a minimum of 1.6 cm in length with multiple sections taken from various levels.

Collection & preparation: Lab to follow standard published protocols for processing of BM biopsy specimen. Fixatives should be available in the BM operation theatres.

Morphology: Obtain good quality thin sections (<3 micron thick). BM trephine sections are stained with H&E stain. Additional stains include Reticulin, Giemsa and an Iron stain. Each slide should be

examined initially for cellularity and trilineage hematopoiesis. Any abnormal infiltrate should be identified and described in terms of cellular morphology and type/pattern of infiltration. Lymphoma infiltration can be in form of one or a combination of the 5 categories including interstitial, paratrabecular, nodular, diffuse pattern and intrasinusoidal. Subtle BM infiltrates may be seen in Anaplastic Large Cell Lymphoma (ALCL), Splenic Marginal Zone Lymphoma (SMZL) (intra sinusoidal infiltrates) etc. and are picked up by IHC.

4. Body fluid samples

Body fluids like cerebrospinal fluid (CSF) and pleural fluid are best examined within 6 hours of collection. As the quantity of CSF is low, selection of IPT panel becomes crucial so as not to miss the cells of interest. Pleural fluids in adolescent are generally involved by T-lymphoblastic lymphomas so accordingly it is important to do cytoplasmic CD3 and Tdt apart from routine stains. Similarly ascitic fluid may show presence of Burkitt's lymphoma or DLBCL. Cytomorphology along with FCM is helpful in such situations.

2.4 Ancillary Techniques

A. Immunophenotyping

All immunostaining should be requested as a panel of antibodies rather than individual tests. Three methods of immunophenotyping that yield the similar information are IHC, FCM and immunofluorescence. It may be expensive to do both IHC and FCM in each case of lymphoma. FCM is best done for blood/ bone marrow/ fluids, while IHC for lymph node and extra nodal lesions. FCM may also be done on FNAC of lymph nodes. Few centers do both flow cytometry as well as IHC regularly in the diagnosis of lymphomas. IPT is performed as a panel rather than an individual marker. Furthermore, understanding of the normal staining pattern and cross-reactions of an antibody is crucial to the correct interpretation and diagnosis. There are markers which work better on IHC like cyclin D1, and other markers which work better on FCM like FMC7. Both these techniques are complementary. All labs doing IPT must have a stringent internal quality control program and also participate in a proficiency testing program. Each new lot of antibody needs to be verified or validated, as required before being used for diagnostic purposes. All laboratories should preferably conform to international quality standards (ISO; 15189) and be accredited by national accreditation agency, NABL (National accreditation board for testing and calibration of laboratories).

1. Immunohistochemistry: Of all the available ancillary techniques, IHC is more widely available tool for diagnosing NHL. Immunophenotyping of lymphomas as B or T cell type is not straight forward as many of them have a polymorphous population. There are more than 250 CD markers available today and approximately 40-45 being routinely used in IHC labs for diagnosis of hematolymphoid neoplasms. It is important to understand reactions of these markers to different cells in the lymphoid organs. A normal LN has many compartments and different types of cells. All these compartments react differently to different antibodies. An example is of bcl-2 reaction in a normal LN. Bcl-2 is commonly used in the differential diagnosis of follicular lymphoma from follicular hyperplasia. It is important to note that in a normal LN, bcl-2 shows positivity with mantle cells, interfollicular T cells and in T cells (CD4+) present within the germinal centres.

Large list of CD markers is available and newer ones are on the way. Histopathologist decides the panel based on morphology, using both individual experience and published literature. Most of the times, diagnosis is established on a morphological examination for the lesion. Accordingly a panel of antibodies is done to confirm and further subtype the neoplasm, to find out predictive markers (CD20 positive B-cell

lymphoma may receive Rituximab therapy), prognostic markers (CD38 and Zap 70 in CLL), and also to differentiate between a benign and a malignant proliferations in the LN (follicular hyperplasia versus follicular lymphoma).

2. Flow cytometry: FCM is particularly useful in cases where there are homogeneous tumour cell populations such as lymphoblastic lymphoma in which terminal deoxynucleotidyl transferase (TdT) can be readily detected or CLL and mantle cell lymphoma where the simultaneous expression of CD5 and CD20 on tumour cell surfaces can be identified (advantages of multicolor IPT). Most labs in India do 3-4 color IPT. The data generated by FCM are not limited to the percentage of cells positive with a marker, but extend to simultaneous expression of markers and the intensity of staining. FCM has its own limitations. Evaluation of possible T-cell rich B cell lymphoma or a HL can be a problem because of scanty tumor cells and also nodal fibrosis which might prevent recovery of Reed-Sternberg cells. Similarly, necrotic tumours can give negative results if the small sample used in the flow analysis for FC does not contain any viable tumor cells.

IHC has an advantage that the histologically abnormal cells can be seen on microscopy to express or lack a particular marker. It may supplement the information generated by FCM and may be the only investigation when FCM is not available. Representative paraffin blocks may be selected for IHC staining. When selecting panels for IHC it is important to include antibodies that are expected to give negative as well as positive results. Most lymphomas are substantially defined by their immunoprofile. When there is a discrepancy between morphology and IPT (technical failure, incorrect diagnosis or a genuinely aberrant result), further investigations are needed to clarify the results. The final report must highlight discrepancies and should suggest an explanation for abnormal or conflicting immunochemical findings.

Immunophenotypic profile of cells of a normal lymph node

It is important for a pathologist to study normal histology along with IHC patterns of LNs biopsied from various sites to understand different compartments and dynamic nature of the LN. Normal LN reveal a spectrum of histological features. Most pathologists have a limited training and experience in hematopathology. Other issues like suboptimal fixation of tissues, inadequate sampling, and unavailability of adequate markers for IHC add to the vows of the pathologists. Immunophenotyping of lymphomas as B or T cell type is not straight forward as many of them lymphomas exhibit a polymorphous population and majority of the cells in the background may be non-neoplastic as seen in T cell rich B cell lymphoma and cHL, etc. Thus, adequate training and experience in hematopathology is essential. Moreover the pathologist must keep him/herself updated by regularly attending Continuing Medical Education (CMEs), meetings on HLN. Normal LN histology biopsied from different sites along with IHC expressions with different markers, must be studied in details to understand different compartments and dynamic nature of the LN.

Immunophenotyping and lymphoma

1. Diagnostic panels for IHC / FCM

a. IHC: Subtle diagnoses that are easily missed on the basis of standard H&E-stained sections include interfollicular HL, sinusoidal infiltration by ALCL, partial nodal involvement by FL or in-situ lymphomas, etc. MCL may morphologically resemble CLL or a blastic leukemia. These should be recognized by careful analysis at light microscopy, but a small panel of antibodies can be useful to correctly identify these cases. Though there is no defined list for minimal markers, a laboratory must have a adequate B, T, Myeloid and other common markers for sub-typing of HLN. Attached is a suggested list of the common antibodies used in lymphoma diagnosis (Table 1).

Table 1: Essential markers for a Hematopathology laboratory
LCA, CD20, CD3, CyclinD1, Tdt, CD34, Mib1, CD10, CD15, CD30, Alk1, Pax5, CD138, kappa and lambda light chains, MPO

Tertiary care centers should aim to do a comprehensive diagnostic work-up as per WHO2008 classification of HLN (Table 2, 3). Smaller labs might have lesser markers in their armamentarium, however, shall refer cases to higher centers for additional IHC markers, as and when need arises. Though there is no list of minimal markers for diagnosis of lymphomas, two levels (based on number of antibodies used) of antibodies may be suggested, first level of best laboratory practice where all markers are available and second level where bare essential markers are available to make a diagnosis in vast majority of cases.

Table 2: Comprehensive panel of antibodies as a lymphoma panel
B-cell lymphoma panels:
CD20, CD79a, CD23, CD10, CD3, CD5, BCL2, BCL6, Ki67, IRF4/Mum1, CD21, CD23, CD35, Cyclin D1, Pax5, Tdt, CD138, CD43, p21, Annexin A1, CD123.
T cell lymphoma panels:
CD2, CD3, CD4, CD5, CD7, CD8, CD56, Ki67, CD23, CD10, CD25, CD30, Alk1, Tdt
Hodgkin lymphoma panels:
LCA, CD3, CD20, CD15, CD30, Pax5, Alk1, IRF4/Mum1, EBV-LMP1, EBE-EBER (ISH), Oct2, Bob1, EMA, CD57
***Miscellaneous*:**
C-kit, CD1a, CD163, CD61/CD41, CD235, CD71
***Other markers*:**
CK, EMA, S-100, HMB45, Melan A, Desmin, Mic2, FLI1, MyoD1, Myogenin, Synaptophysin, Chromogranin, ER, PR, Cerb b2

Table 3: Different lymphoma subtypes and panels	
Suggested basic panel for any hematolymphoid lesion is LCA, CD20 and CD3. For blastic lymphoid cell proliferations CD79a and CD19 are better markers than CD20. Additional panel for other circumstances (based on morphological impression):	
Small cell lymphomas	CD5, CD23, cyclin D1 bcl-6, CD10, CD43, bcl2
Burkitt's lymphoma	bcl2, MiB1, CD10
Lymphoblastic lymphoma	CD99, TdT, CD79a
ALCL	CD30, ALK-1, EMA
PTCL	CD56, CD30, ALK1, CD23, CD10, CD4, CD8, Tdt
Suspected NK cell lymphoma	CD56 (Others: CD8, TIA-1, granzyme B)
Cutaneous lymphomas	CD3, CD20, CD4, CD8, CD10, CD30
EBV related lymphomas	EBER by in-situ hybridization
Histiocytic differentiation	PGM1 (CD68), CD163, CD1a
Dendritic cell	CD21, CD23, CD35, S-100
Classical HD	LCA, CD15, CD30, CD15, Pax5
NLPHL	CD20, CD3, CD56, Oct2, Bob1
Plasma cell dyscrasias	CD79a, CD38, CD138, k/l light chains, EMA, Mum1, cyclinD1, CD19
Granulocytic sarcoma	CD43, MPO, cKit

The laboratory may further have a policy to use a smaller primary panel based on morphology, do a more elaborate secondary panel depending on the findings of primary panel, else laboratory might have a policy of doing a comprehensive panel upfront. In many cases, a small primary panel may suffice, example, LCA, CD3 and CD20 in a case suspected to be a lymphoma. In case the tumor cells

express CD20, the laboratory may do secondary panel (depending upon morphology) which may include at least Mib1, CD10 and bcl2 to differentiate DLBCL from BL and cyclinD1 may be used to differentiate mantle cell lymphoma from other low grade lymphomas.

Various lymphoma subtypes may look similar on morphology and may also mimic other tumors like a carcinoma, melanoma or even a round cell tumor. Moreover, pathologist will not know what is going to be on his/her table next. Few common morphological mimics include HL and ALCL or a T cell histiocyte rich B cell lymphoma, nasopharyngeal carcinoma and DLBCL, plasmablastic lymphoma and malignant melanoma and lymphoblastic lymphoma and any other round cell tumor. Many of B-cell lymphomas like plasmablastic lymphomas might not express CD20, thus highlighting requirements of more extensive panels like Mum1 and CD79A. Moreover, Alk1 classically expressed in ALCL may also be expressed in large B cell lymphomas as is cyclin D1 which may be expressed in hairy cell leukemia and plasma cell dyscrasia apart from mantle cell lymphoma.

b. Flow cytometry immunophenotyping: Immunophenotyping by FCM is the most reliable and robust test for the diagnosis of chronic lymphoproliferative disorders (CLPDs) in peripheral blood (Table 4). It is performed virtually in all cases with lymphocytosis to confirm the diagnosis (suspected by Peripheral Blood Smear (PBS) morphology) and to further subtype the disorders[4]. Most of these are B-cell phenotype, common subtypes include chronic lymphocytic leukemia followed by follicular lymphoma, mantle cell lymphoma, hairy cell leukemia, Waldenstrom's macroglobulinemia, splenic marginal zone lymphoma, and the rarer T cell CLPDs which may include T/NK large granular cell leukemia, T cell prolymphocytic leukemia, Sezary syndrome, Adult T-cell leukemia/lymphoma etc. Thus immunological markers will allow the separation of B- from T-cell-derived diseases and, within the B-cell conditions, will establish the clonal nature of the lymphocytes by showing Ig light chain restriction and subtype CLPDs based on morphology and immunoprofile. Documentation of B-cell clonality (by doing light chain restriction) in cases with borderline lymphocytosis is important to differentiate neoplastic, clonal B-cell disorders from benign conditions. It is important to note that clonality is not equivalent to malignancy.

Table 4: Common markers used in a FCM laboratory for lymphoma diagnosis

B cell markers	CD19, CD20, CD23, FMC7, CD10, K/L light chains, CD79b, CD11c, CD25, CD103, CD123
T cell marker:	CD2, CD3, CD4, CD5, CD7, CD8, TCR a/b, TCR g/d
NK cell associated markers	CD16, CD56, CD57, CD94
Plasma cell markers	CD38, CD138
Others	HLADR, Tdt, CD34, antiMPO

B. Diagnostic panels for Cytogenetic and FISH studies

Specific chromosome abnormalities are strongly associated with particular subtypes. e.g. t(8;14) or variants in Burkitt's lymphoma and t(11;14) in Mantle cell lymphoma. These specific translocations can be detected by FISH or PCR. Several cytogenetic abnormalities, including chromosomal translocations and trisomies, have been described in MALT lymphoma, and two translocations [t(11;18)(q21;q21) and t(1;14)(p22;q32)] are associated with resistance to conservative treatment.

The preferred tissue for cytogenetic analysis of lymphoma is nearly always involved LN, spleen or other primary disease tissue. BM even when heavily involved might yield only normal metaphases and peripheral blood samples often fail to yield mitoses, particularly in low grade lymphomas. If cytogenetic analysis is attempted using BM, a substantial number of cells should be screened for obvious lymphoma-associated abnormalities.

Cytogenetic and FISH analyses are more useful at the time of diagnosis, than during disease monitoring, as they are sensitive in LN/ spleen and relatively insensitive in blood and bone marrow. Molecular monitoring of a known detectable translocation is much more sensitive, although FISH will pick up a higher proportion of cases with standard translocations at diagnosis.

C. Diagnostic panels for Molecular tests

The use of PCR for specific translocations such as t(14:18), BRAF mutations in Hairy cell leukaemia and for detection of T-cell receptor clonality and B-cell clonality, based on T-cell receptor and immunoglobulin heavy and light chain gene rearrangement studies, are important diagnostic tests. However, false positives and negatives are not uncommon. The results of the cytogenetic and molecular tests should be interpreted with other morphological and immunoarchitectural features eg: t(8;14) is seen not only in Burkitt's lymphoma but also in DLBCL. Therefore, PCR results should not form the sole basis for a diagnosis.

2.5 Reporting and checklist for reporting lymphoma

Data generated from all modes of investigation need to be collated and interpreted in a clinical context. For some diseases, an accurate history may be essential to diagnosis; e.g., post-transplant-associated lymphoproliferative disease.

Provisional report may first be released followed by a final impression along with IHC findings. Supplementary report shall follow in case molecular studies/ FISH are performed. Kindly note that lymphoblastic lymphoma and Burkitt's lymphoma are oncological emergencies and an early provisional report must be given to the pediatric oncologist. Turn around time for a lymphoma histopathology report may be 3-4 working days and 7-8 days when IHC has been performed.

- Classification according to WHO 2008.
- T or B cell phenotype (CD20 positive or negative).
- Incorporate IHC in the final report. Mention about the reaction of IHC with the tumor cells and also the reactive cells in the background. All stains done should be reported.
- Incorporating results of other ancillary techniques.

2.6 Disposal of tissues

Each laboratory shall follow the local/national laws for waste management/disposal for remaining specimen, used reagents, garbage, infectious waste etc. Retention period for tissues may be at least 2 months from the date of dispatch of the final report. These specimens are taken out, formalin is discarded and tissue may be wrapped in appropriate containers which may be given to authorized agencies for disposal/ incineration. Chemicals like 10% buffered formalin; xylene and alcohols are hazardous and are discarded as per waste disposal policy of the laboratory.

2.7 Storing specimens

No diagnostic material should be discarded until all investigations are complete. NABL recommends that paraffin blocks are stored for a minimum of 20 years. Stained slides should be stored for a minimum of 10 years, and preferably longer, especially in the case of pediatric cases and in small biopsy specimens where material permitting diagnosis may no longer be contained within the paraffin blocks.

2.8 Fine needle aspiration cytology (FNAC)

Cytology is an easy, simple and cheap technique, extremely popular amongst cytopathologists. Experienced cytologists offer an extremely high degree of reliability. It may be used in diagnosing

recurrence of lymphomas. FNA material may be used for FCM and Molecular tests. Cytologist should avoid making lymphoma diagnosis on FNAC examination alone. Lymphoma diagnosis is best done on a biopsy and FNAC is not recommended to diagnose lymphomas. In context of lymphomas, FNAC may be useful in the following circumstances:

1. In a known case of lymphoma, for documentation of relapse.
2. Emergency cases as patient having a mediastinal mass and superior vena cava syndrome. FNAC may be performed before instituting therapy. The sample may be send for morphology and for FCM. Biopsy should still be advised for proper typing of lymphoma.
3. FCM immunophenotyping (IPT) is performed for diagnosis and subtyping of HLN, however, subtypes (like HL) may be missed by this technique.
4. FCM may be used to establish a primary diagnosis of hematolymphoid neoplasm when there is no other readily available tissue. In difficult cases where the biopsy interpretation is inconclusive, FCM might provide invaluable additional information as elaborate markers are available for FCM. On the contrary, diagnosis and subtyping of myeloid neoplasm and chronic lymphoproliferative disorders (CLPDs) is best done by FCM.
5. FNAC may be performed in suspected cases of tuberculosis.

2.9 SOPs for laboratories for tissue processing

1. Sample accession
2. Grossing procedure: As per standard grossing manuals
3. Fixation
4. Decalcification
5. Tissue processing
6. Embedding
7. Routine staining (Hematoxylin and Eosin)
8. Mounting procedure
9. Submission of slides
10. Reporting of results (Text, Comment, Impression, Signature)
11. Procedure for telephonic reporting
12. Procedure for handling pending reports
13. Slide and block filing
14. Discarding of slides & blocks
15. Medical records
16. Special stains (AFB, GMS, PAS, Congo red, Reticulin, Perl's, Giemsa etc)
17. IHC
18. Karyotyping and FISH studies
19. Molecular studies
20. Internal quality control
21. Proficiency testing program

CHAPTER

3 STAGING

3.1 Staging work-up

Clinical

- Clinical history with reference to B symptoms and family history
- Physical examination with particular attention to node-bearing areas, Waldeyer's ring, and size of liver and spleen
- Performance status (ECOG) including co-morbidity

Haematology

- CBC, differential and film
- Bone marrow aspirate and trephine
- Cytogenetics and Immunophenotyping of marrow +/- blood in low grade lymphomas and any other lymphomas with morphological evidence of marrow/blood involvement

Biochemistry

- LDH, urea and electrolyte, creatinine, albumin, aspartate transaminase (AST), bilirubin, alkaline phosphatase, serum calcium, uric acid
- Pregnancy test in females of child-bearing age

Serology

- Hepatitis B and C, HIV status

Radiology

- CXR
- Chest and abdominopelvic computed tomography (CT) with oral and intravenous contrast (unless coexistent renal insufficiency)

Staging work-up (sometimes indicated)

Radiology

- Plain bone X-ray and bone scintigraphy
- Neck CT
- Head CT or magnetic resonance imaging (MRI)
- PET scan: FDG-PET scan has been used for initial staging, restaging and follow up of patients with NHL. PET shows a high positivity and specificity when used for staging and restaging of lymphomas.

PET scans should be used in conjunction with diagnostic CT scans. Integrated PET-CT has largely replaced the CT scan.

Haematology

- Coagulation screen
- ESR
- DCT

Biochemistry

- Serum immunoglobulins/electrophoresis
- Beta 2 microglobulin
- CRP
- Tissue transglutaminase test (tTG) to exclude coeliac disease

Serology

- EBV, HTLV serology

Molecular genetics

- FISH or PCR on involved marrow/blood for specific lymphoma-associated translocations
- IgH and TCR rearrangements on marrow/blood if molecular staging clinically indicated

Others

- MUGA scan or echocardiography is recommended when anthracycline containing regimens are used.
- Endoscopy and endoscopic ultrasound head CT scan or brain MRI and lumbar puncture depending on suspicion of extranodal involvement.
- Lumbar puncture if lymphomatous meningitis is suspected or if indications for prophylactic treatment are present. CNS prophylaxis is currently used in patients with Burkitt Lymphoma, lymphoblastic lymphoma, HIV-related lymphoma, HTLV-1 related lymphoma and post-transplant lymphoproliferative disease. About 5% of patients with DLBCL develop CNS disease. Patients at increased risk of CNS relapse (those with involvement of the paranasal sinuses, testes, bone-marrow involvement with large cells or having two or more extra-nodal sites with elevated LDH).

3.2 Staging of Lymphoma

The stage of lymphoma is of major therapeutic and prognostic significance in the management of lymphoma. The staging system used for adult high grade lymphomas is based on the Ann Abor system.

Ann Arbor staging classification for NHL

Stage	Area of involvement
I	One lymph node region
IE	One extralymphatic (E) organ or site
II	Two or more lymph node regions on the same side of the diaphragm
IIE	One extralymphatic organ or site (localised) in addition to criteria for stage II
III	Lymph node regions on both sides of the diaphragm
IIIE	One extralymphatic organ or site (localised) in addition to criteria for stage III
IIIS	Spleen (S) in addition to criteria for stage III
IIISE	Spleen and one extralymphatic organ or site (localised) in addition to criteria for stage III
IV	One or more extralymphatic organs with or without associated lymph node involvement (diffuse or disseminated); involved organs should be designated by subscript letters (P, lung; H, liver; M, bone marrow)
A = asymptomatic;	
B = symptomatic; unexplained fever of ≥38°C; unexplained drenching night sweats; or loss of > 10% body weight within the previous 6 months).	
X = Bulky tumor is defined as either a single mass of tumor tissue exceeding 10 cms in largest diameter or a mediastinal mass exceeding 1/3 of the transverse maximal transthoracic diameter.	

CHAPTER

4 PERFORMANCE INDEX

4.1 ECOG performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self care. Totally confined to bed or chair
5	Dead

4.2 International Prognostic Index (IPI)[5]

The IPI is a prognostic model based on 5 parameters

SCORE	0	1
Age (years)	< 60	≥ 60
Performance Status	0 – 1	2 – 4
Stage	I – II	III – IV
LDH	N	≥ N
Extranodal sites	≤ 1	> 1

Based on these factors, patients with DLBCL can be divided into 4 prognostic categories as summarised below:

IPI risk group	IPI Score	CR Rate (%)	5 year overall survival (%)
Low-risk	0,1	87	73
Low/intermediate-risk	2	67	51
High/intermediate-risk	3	55	43
High risk	4, 5	44	26

The IPI describes a predictive model for patients with DLBCL at presentation.

It has been adjusted for use in Follicular Lymphoma (FLIPI) and is less useful in Anaplastic Large Cell Lymphoma, mediastinal B cell lymphoma and T-NHL.

It should not be used in Burkitt lymphoma or lymphoblastic lymphoma.

4.3 Age adjusted International Prognostic Index (aa-IPI)

Risk factors for age adjusted IPI are ECOG performance status 2, Stage III/IV, and LDH >ULN

aaIPI risk group	aaIPI Score	5 year overall survival (%)
Low-risk	0	83
Low/intermediate-risk	1	69
High/intermediate-risk	2	46
High risk	3	32

4.4 Revised International Prognostic Index (R-IPI)

In the Rituximab era the IPI has been revised and the patients are grouped as follows:

IPI Score	Outcome	Overall Survival
0	Very Good	94%
1-2	Good	79%
3, 4, 5	Poor	55%

4.5 Mantle Cell -International Prognostic Score (MIPI)6

Points	Age (years)	ECOG PS	LDH- ULN	WBC- 10 x^9/L
0	<50	0-1	<0.67	<6.700
1	50-59	-	0.67-0.99	6.700-9.999
2	60-69	2-4	1.0-1.49	10.000-14.999
3	≥70	-	1.5	15.000

ECOG PS - Eastern Cooperative Oncology Group performance status;
LDHULN - lactic acid dehydrogenase institutional upper limit of normal;
WBC - white blood cell count from the complete blood count
*Each patient can have a maximum of 11 points derived from each of the 4 parameters.
Patients with 0-3 points are classified as low risk, 4-5 points are intermediate risk, and 6 points are high risk.

CHAPTER

5 RESPONSE EVALUATION

Response should be evaluated with radiological evaluation after 3- 4 cycles and at the end of treatment. Infiltration of marrow or CSF at diagnosis needs to be rechecked at the end of treatment.

5.1 Response Criteria not including PET[7]

Response category	Physical examination	Lymph Nodes	Lymph Node masses	Bone Marrow
Complete Remission (CR)	Normal	Normal	Normal	Normal
Complete Remission unconfirmed (CRu)	Normal Normal	Normal Normal	Normal/ >75% decrease	Normal Normal/ Indeterminate
Partial Remission (PR)	Normal Normal Decrease in size of liver/spleen	Normal >50% decrease >50% decrease	Normal >50% decrease >50% decrease	Positive Irrelevant Irrelevant
Relapse/Progression	Enlarging liver/spleen	New or increased	New or increased	Reappearence

5.2 Response Criteria including PET[8]

Response category	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Complete Remission (CR)	Disappearence of all evidence of disease	a) FDG –avid or PET positive before therapy; mass of any size permitted if PET negative b) Variably FDG- avid or PET-negative; regression to normal size	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative.
Partial Remission (PR)	Regression of measurable disease and no new sites	>50% decrease in SPD of upto 6 dominant masses; no increase in size of other nodes a) FDG-avid or PET positive before therapy; >1 PET-positive at previously involved site. b) variable FDG avid or PET negative; regression on CT	>50% decrease in SPD of nodules; no increase in size of liver or spleen.	Irrelevent if positive before therapy; cell type should be specified

Stable Disease (SD	Failure to attain CR/ PR or PD	a) FDG-avid or PET-positive before therapy; PET-positive at prior site of disease and no new site on CT or PET b) variably FDG-avid or PET-negative; no change in size of previous lesions on CT	x	x
Relapse/ Progressive disease (PD)	Any new lesion or increase by >50% of previously involved sites	Appearance of new lesion(s) >1.5 cms in any axis, >50% increase in SPD of more than one node, or > 50% increase in the longest diameter of previously identified node >1cm in short axis. Lesions PET-positive if FDG-avid lymphoma or PET-positive before therapy.	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CHAPTER

6 TREATMENT REGIMENS

Treatment of high grade lymphomas is based on histologic subtype, extent of disease, and age of the patient. In the case of discordant (two separate sites of disease with differing lymphoma types), composite (one site of disease with two discrete types of lymphoma at that site) or transformed (a second lymphoma developing out of a background of previously known lymphoma) lymphoma, treatment must be directed at the most aggressive phase of the disease.

6.1 Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% of NHLs diagnosed. Transformed DLBCL, Follicular lymphoma grade 3B, Intravascular DLBCL, ALK positive DLBCL, EBV positive DLBCL, T-cell/histiocyte rich large cell lymphoma are also managed according to the DLBCL guidelines.

Clinical Presentation

DLBCL can present with nodal or extranodal disease, with up to 40% of cases presenting with extranodal disease. The most common extra-nodal site is the gastrointestinal tract (mainly stomach and ileocaecal region) but the disease can present at virtually any location including skin, central nervous system (CNS), bone, testis, soft tissue, salivary gland, female genital tract, lung, kidney, liver, Waldeyer's ring and spleen. Primary presentation with bone marrow or peripheral blood involvement is rare.

Primary mediastinal large B-cell lymphoma differs in that the disease is limited to the mediastinum and is seen more frequently in women between 20-40 years. Patients typically present with a single, rapidly enlarging mass which on staging may be more disseminated.

Transformed DLBCL following an indolent lymphoma such as chronic lymphocytic leukaemia/ small lymphoctic lymphoma (CLL/SLL), follicular lymphoma, marginal zone B-cell lymphoma or lymphocyte predominant Hodgkin lymphoma is well described. Underlying immunodeficiency and auto-immune diseases are significant risk factors and are frequently associated with Epstein-Barr virus (EBV) positivity.

Pathology

DLBCL replaces the normal architecture of the lymph node or tissue of origin diffusely, though the infiltration can be partial, inter-follicular or rarely sinusoidal. The perinodal soft tissues are often infiltrated. DLBCLs are morphologically diverse including a number of specific subtypes and specific entities (see below) and a large number of cases which are grouped together as DLBCL not otherwise specified (NOS). DLBCL NOS includes the common morphologic variants centroblastic, immunoblastic and anaplastic in addition to rare morphologic variants. DLBCL NOS can also be divided into subgroups based on immunophenotype (CD5+, Germinal centre B cell-like (GCB), non-GCB) or based on gene

expression profile [Germinal center B cell-like (GCB) and activated B cell-like (ABC)], although use of these subgroups to determine therapy is not currently recommended.

Specific subtypes of DLBCL include T cell/histiocyte rich DLBCL, Primary CNS DLBCL, Primary cutaneous DLBCL (leg type) and EBV positive DLBCL of the elderly.

Specific DLBCLs with characteristic clinicopathological features include Primary mediastinal large B cell lymphoma, Intravascular large B cell lymphoma, DLBCL associated with chronic inflammation, Lymphomatoid Granulomatosis, ALK-positive large B cell lymphoma, Plasmablastic lymphoma, Primary effusion lymphoma and Large B cell lymphoma arising in HHV-8 associated Castleman's disease.

Immunophenotype

DLBCL express pan-B markers including CD19, CD20, CD22 and CD 79a. Surface and/or cytoplasmic immunoglobulin (IgM>IgG>IgA) can be demonstrated in 50-75% cases. CD30 is expressed in some with anaplastic morphology. Some cases of DLBCL (<10%) express CD5, most of which represent de novo DLBCL rather than transformation from CLL/SLL. CD5 +ve DLBCL is cyclin D1 –ve, allowing differentiation from blastoid mantle cell lymphoma. CD10 is expressed in 30-60% cases, BCL6 in 60-90%, BCL2 in 30-50%, and IRF4/MUM1 in 35-65% cases (IRF4/MUM1 and BCL6 co-expression may be present). Immunophenotypic subgrouping of DLBCL is based on expression of CD10/BCL6/IRF4/MUM1.

The proliferation fraction, measured by Ki-67 staining is usually high (>40%) and may be greater than 90% in some cases.

Genetics

The t(14;18)(q32;q21) occurs in 20-30% cases, up to 30% show abnormalities of the 3q27 region involving BCL6. Microarray studies have shown two major molecular categories of DLBCL with germinal centre (GC) and activated B cell (ABC) patterns suggestive of malignant transformation at different stages of B-cell development.

The immunophenotypic profile of GC DLBCL is CD10+ve, BCL6+ve and the ABC pattern is usually CD10-ve, BCL6-ve and BCL2+ve.

Staging

As for other aggressive lymphomas.

Treatment

Treatment options vary between patients with localized (stage I-II) and advanced (stage III-IV) disease. Prognosis is extremely good for patients with no adverse risk factors (Normal LDH, stage I or II non-bulky disease, age less than 60 years or ECOG performance status less than 2).

Stage I-II

For patients with Non-bulky (<10 cm) stage I or II disease, CHOP +/- Rituximab (R) for 3 cycles with IFRT or 6 cycles of CHOP +/- R alone is recommended (Category 2A).

Patients with bulky disease (10 cm or more) should be treated with 6 cycles of CHOP+/-R with or without IFRT (Category 1).

CHOP +/- R for 3 cycles followed by involved field radiation therapy (IFRT) has been the standard treatment for patients with stage I-II based on the results of the SWOG 8736 study[9], in which 3 cycles

of CHOP with IFRT produced significantly better progression-free survival (5-yr PFS: 77% vs 64% for 3 cycles of CHOP alone). The efficacy of the addition of rituximab to CHOP and IFRT has also been reported in the SWOG 0014 study[10] (CHOP– R for 3 cycles followed by IFRT). The results in this trial were favorable in comparison to historical results (4-year PFS 88% vs 78% in historical controls).

Stage III-IV

For patients with advanced stage disease, treatment with 6 cycles of CHOP+/-R repeated every 21 days is recommended (Category 1).

In selected cases, RT to bulky sites may be beneficial (Category 2B).

Patients at increased risk of CNS relapse (those with involvement of the paranasal sinuses, testes, bone-marrow involvement with large cells or having two or more extra-nodal sites with elevated LDH) should receive CNS prophylaxis with 4-8 doses of Intrathecal methotrexate or 3-3.5 Gm/M2 of systemic methotrexate.

In pre-rituximab era, CHOP was compared with various intensive chemotherapies and found to be equally effective, thus remained preferred treatment[11]. Presently CHOP+/-R chemotherapy is standard treatment for patients with advanced stage DLBCL based on the results of the GELA LNH98-5 study in elderly patients. Long-term follow-up of this study showed that PFS (36.5% vs 20%), DFS (64% vs 43%), OS (43.5% vs 28%) rates were significantly in favor of R-CHOP at the median follow-up of 10 years[12]. These results have been confirmed by many other randomized trials[13-15]. No clinical benefit of maintenance rituximab in first remission was demonstrated in the ECOG/CALGB 9703 study[16]. Various trials failed to show clinical benefit of dose-dense therapy (R-CHOP-14) in comparison to CHOP+R-21[17]. R-CHOP-14 may also be acceptable in selected circumstances (Category 2B).

Doxorubicin in CHOP regimen can be replaced with etoposide, liposomal doxorubicin or mitoxantrone in patients with poor left ventricular function (Category 2B).

Patients with bulky disease or impaired renal function should be monitored for tumor lysis syndrome.

The studies evaluating the role of upfront high dose therapy followed by autologous stem cell rescue (HDT/ASCR) failed to show significant benefit to upfront HDT/ASCR as compared with first line rituximab-based chemoimmunotherapy. Presently, upfront HDT/ASCR is recommended only in selected high-risk circumstances (Category 2B).

Response Evaluation

Response should be evaluated with radiological evaluation after 3- 4 cycles and at the end of treatment. Infiltration of marrow or CSF at diagnosis needs to be rechecked at the end of treatment. Patients who are not PET negative at the end of treatment have primary refractory disease and should be considered for salvage therapy.

Follow Up: As for other aggressive lymphomas.

6.2 Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a B-cell neoplasm composed of monomorphic small to medium sized lymphoid cells with irregular nuclei which most closely resemble centrocytes/ follicle centre cells but with less-irregular nuclei. MCL accounts for 6% of all newly diagnosed cases of NHL

Clinical Presentation

Patients usually present with enlarged LNs at multiple sites and frequently have a massively enlarged spleen. Bone marrow involvement with occasional leukaemic spill is present in 80% patients. Waldeyer's Ring and the gastrointestinal tract are frequent extra-nodal sites of involvement and have been reported in 15-30% patients with MCL. Lymphomatous polyposis of the gastrointestinal tract is a form of mantle cell lymphoma and can occur as variably-sized polyps in any part of the gastrointestinal tract.

Pathology

MCL shows architectural destruction by a monomorphic lymphoid proliferation with a vaguely nodular or mantle zone growth pattern. Many cases have scattered single epithelioid histiocytes which can produce a 'starry sky' appearance. Hyalinized small blood vessels are commonly seen. Disease progression or relapse is characterised by an increase in nuclear size, pleomorphism, nuclear chromatin dispersal and an increase in mitotic activity. Blastoid variants with cells resembling lymphoblasts and a high mitotic index are associated with a worse prognosis.

Immunophenotype

The neoplastic cells are monoclonal B-cells with intense surface IgM+/- IgD. They are CD19+ve, CD20+ve, CD5+ve, FMC7+ve and CD10-ve and express Cyclin D1. Cases with gastrointestinal involvement express the alpha4 B7 homing receptor.

Genetics

MCL is defined by the presence of the t(11;14)(q13;q32) resulting in juxtaposition of Cyclin D1 and the IgH gene which leads to upregulation of Cyclin D1. The translocation can be detected reliably by FISH and in about 40% of cases by PCR.

Staging

Staging of disease, if nodal, can be reported using the Ann Arbor classification, but is clearly not appropriate for extranodal presentation such as multiple lymphomatous polyposis.

Investigations

In addition to investigations for aggressive lymphoma, gastrointestinal endoscopy (if appropriate) and BMA and trephine, with immunophenotyping and FISH / PCR if marrow involved.

Treatment

Stage I-II

Very few patients present with localized MCL. Local RT (30-36Gy) alone or combination chemo-immunotherapy is recommended (Category 2A).

If the patient received initial treatment with RT alone and relapses after CR, then the patient can be treated with first-line induction chemo-immunotherapy[18].

In a retrospective analysis of patients with limited-stage non-bulky disease (stage IA or IIA), inclusion of local RT with or without chemotherapy was associated with significantly improved progression-free survival (PFS) at 5 years (68% versus 11%)[19].

Stage II (bulky) and stage III-IV

The majority of patients with MCL will have advanced stage disease and require systemic therapy. In highly selected patients with asymptomatic disease, close observation without any therapy is a reasonable

option, especially for those with good performance status and lower IPI[18]. The standard treatment regimen for MCL is not yet established.

Majority of regimens except R-Hyper-CVAD included first line consolidation with HDT/ASCR in published reports.

Most commonly used aggressive therapies are Hyper-CVAD +/- R[20,21] or high dose Ara-C based regimens and less aggressive therapies are CHOP+/-R[22,23] or Bendamustine and rituximab[24].

For patients with CR to first line therapy, consolidation with HDT/ASCR is recommended for young eligible patients.

For patients with only PR to first line therapy, second line therapy may be considered in an effort to improve the quality of a response.

For patients who relapse after achieving a remission to first line therapy or for patients who experience disease progression during therapy, second-line treatment options can be considered.

For patients who are not candidates for HDT/ASCR and are in remission after first line therapy with R-CHOP, maintenance treatment with rituximab is recommended[25].

Second line options include Bendamustine +/- rituximab, Bortezomib +/- rituximab, Fludarabine based therapy or Lenalidomide+/-rituximab.

Myeloablative or reduced intensity allogenic transplantation is an appropriate option for patients who are in remission after second-line therapy[26].

6.3 Burkitt's lymphoma and Burkitt leukaemia (ALL-L3)

Burkitts' Lymphoma (BL) is a rare lymphoma in adults, except in HIV positive patients. It constitutes 1% to 2% of all non-HIV adult lymphomas in Western Europe and the United States.

Clinical Presentation

The World Health Organization (WHO) classified BL on the basis of geographic distribution and clinical presentation into three subtypes: endemic, sporadic, and immunodeficiency-associated BL. These subtypes share the same morphologic and immunohistologic features.

Burkitt's lymphoma has a very high proliferative rate and patients often present with a short history and with large, rapidly enlarging masses. Burkitt-like lymphoma, a condition formally classified as a form of diffuse large B cell lymphoma seems to behave more like Burkitt's and it should be treated as such. In the new WHO lymphoma classification, it is classified with Burkitt's lymphoma.

A leukaemic form of the disease also occurs and this was formally classified as a form of acute lymphoblastic leukaemia (FAB: L3) and treated as such. It is now clear that this is biologically indistinguishable from Burkitt's lymphoma and should be treated in the same way. If ALL therapy is initiated, it should be changed to Burkitt lymphoma therapy when the diagnosis is made.

Pathology

Classical BL is composed of medium sized cells, with round nuclei, clumped chromatin and numerous nucleoli. The cytoplasm is deeply basophilic and usually contains lipid vacuoles. There is a high proliferation rate with numerous mitotic figures and "starry sky" pattern due to the presence of numerous benign macrophages which have ingested apoptotic tumour cells. In Burkitt Leukaemia, more than 30% of nucleated cells should be lymphoid blasts, the characteristic L3 is usually seen.

Immunophenotype

Tumour cells express membrane IgM with light chain restriction and B-cell associated antigens such as CD 19, 20 and 22. CD10 and BCL6 are also expressed. The cells are negative for CD5, CD23 and BCL2. A very high growth fraction is observed and nearly 100% of cells are positive for Ki 67. Infiltrating T-cells are rare.

The blast cells of BL presenting as leukaemia have a mature B-cell phenotype with surface Ig, light chain restriction and expression of CD10, CD19, CD20, CD22 and CD79a, but not TdT. Most cases will fulfil these criteria, but in difficult cases, Ki-67 staining of trephine biopsies (more than 95% positivity) will support the diagnosis.

Genetics

Burkitt lymphoma is defined by translocation of MYC at band q24 to chromosome 14 q32 (t(8;14)) or less commonly to light chain loci at 2q11 or 22q11 leading to MYC over–expression. In endemic cases, the breakpoint on chromosome 14 involves the heavy chain joining region (early B-cell) whereas in sporadic cases, the translocation involves the Ig switch region (later stage B-cell). EBV genomes can be demonstrated in most endemic cases, 20- 40% of immunodeficiency BL and <30% of sporadic BL.

Staging

St Jude modification of Ann Arbor

	Stage Definition
I	A single tumour (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen.
II	A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours + regional node involvement on the same side of the diaphragm. Primary gastrointestinal tract tumour, usually in the ileocaecal area + involvement of associated mesenteric nodes only.
IIR	Completely resected abdominal disease.
IIIA	Two single (extranodal) tumours on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All primary intrathoracic tumours (mediastinal, pleural, thymic). All paraspinal or epidural tumours, regardless of other tumour sites. All extensive primary intra-abdominal disease.
IIIA	Localized but non-resectable abdominal disease.
IIIB	Widespread multiorgan abdominal disease.
IV	Any of the above with initial CNS and/or bone marrow involvement (25%).

Prognostic factors/index: A working modification of the St Jude's staging developed by Magrath is as follows:

Low risk

Stage I, II disease
ECOG 0-2
No tumour mass 10 cm
Normal LDH level

High risk

All other patients

Investigations

In addition to investigations for aggressive lymphoma, all patients need LP and CSF evaluation; Bone marrow aspirate and biopsy with immunophenotype and cytogenetics and EBV serology

TREATMENT

A strategy, developed in children, using brief very intensive chemotherapy can produce long term survival in approaching 90% of adult patients, including patients with bone marrow and CNS involvement[27,28].

There is a high incidence of tumour-lysis syndrome and measures should be taken to prevent and treat this complication.

Patients with bulky disease and organ dysfunction may be treated with modified dose therapy (e.g. 'mini-CHOP'), in an attempt to modify the effects of tumour lysis. They will proceed to more intensive therapy as outlined below.

All patients will require a PICC line or Hickman catheter which should be inserted at the earliest opportunity.

The patient should be treated using one of the brief, high intensity therapies that have been developed for this disease:

- CODOX-M/ IVAC (National Cancer Institute protocol 89-C-41)[27,29,30]
- The BFM protocol (B-NHL 86)[31]
- LMB-86 protocol[28]
- R-HyperCVAD[32]
- CALGB 9251[33]

These protocols include strategies for the treatment of patients with CNS disease at diagnosis.

First relapse

CNS relapse either on or off treatment should be treated in the same way as CNS disease at presentation plus cranial radiotherapy (30 Gy over 3 weeks).

A total of 4 courses of therapy should be delivered after relapse (if using the CODOX-M/ IVAC regimen).

Relapse elsewhere is generally associated with poor prognosis, salvage can be attempted an alternative regimen e.g. a platinum-containing regimen followed by autologous or allogeneic stem cell transplantation if remission is achieved. This should proceed without any delay.

CODOX-M/IVAC protocol[29]

- Three cycles of CODOX-M for low risk patients: single extra-abdominal mass or completely resected abdominal mass and normal serum LDH
- Total 4 cycles of CODOX-M/ IVAC for high risk patients: do not meet low risk Radiotherapy for CNS disease and testicular involvement

6.4 Lymphoblastic lymphoma

Lymphoblastic lymphoma (LBL) is a rare disease that represents only <2% of non-Hodgkin lymphoma (NHL) in adults. The majority of patients are young men with T-cell phenotype. T-LBL is a clinically aggressive disease with frequent involvement of extra-nodal sites, particularly the bone marrow and CNS.

Clinical Presentation

Patients usually present with short history of increasing dyspnoea secondary to a rapidly-evolving mediastinal mass associated with a high leukocyte count. Other sites involved include lymph nodes, liver, spleen, skin, Waldeyer's ring, and gonads.

Pathology

The lymph node architecture is effaced by a monomorphic population of lymphoblasts. The lymphoblasts are medium sized with a high nuclear–cytoplasmic ratio, irregular nuclei, fine chromatin and inconspicuous nucleoli.

Immunophenotype

T-ALL/T-LBL is always TdT positive. Pan T markers including CD3, 4, 5, 7 and 8 are variably expressed with cytoplasmic CD3 and CD7 most commonly expressed. Co-expression of CD4 and CD8 may occur.

Genetics

One third of T-ALL/T-LBL have translocations involving the T-Cell Receptor (TCR) loci at 14q11 (TCR alpha and delta), 7q35 (TCR beta) and 7p14 (TCR gamma). Translocation partner chromosomes include 8q24 (MYC), 1p32 (TAL1) and others. Also, 25% of cases have TAL1 dysregulation either by translocation or microscopic deletion. More than 30% have del (9p) resulting in loss of the tumour suppressor gene CDKN2A, an inhibitor of the cyclin-dependent kinase CDK4.

Investigations

In addition to investigations for aggressive lymphoma, all patients need CSF analysis to exclude meningeal disease and BMA to be assessed by morphology and immunophenotype. If the marrow is morphologically involved, cytogenetics is mandatory.

Treatment

Patients with LBL have typically been treated with regimens appropriate for acute lymphoblastic leukaemia (ALL). The therapeutic regimens for adult patients with LBL are based on the treatment protocols designed for ALL and often include various phases of treatment including induction, consolidation/ intensification, and maintenance.

Patients with systemic LBL can be treated with any one of the chemotherapy regimens (MCP-841, CALGB 8811, GMALL T-ALL, LMB-86 regimen or hyper-CVAD)[34-37]. Patients with CR to induction therapy should be continued with other components of the treatment protocols. It is important that patients be treated with a given treatment protocol in its entirety and not be treated with different components taken from different protocols.

High dose therapy (HDT) followed by autologous stem cell transplant (ASCT) has also been investigated as consolidation. Patients in first remission were randomized to receive consolidation with HDT/ASCT or continuation of conventional chemotherapy and maintenance[38]. The use of HDT/ASCT was associated

with a trend toward improved relapse-free survival (3yr rate: 55% vs 24%) with no improvement in overall survival (OS).

Patients with relapsed disease should be considered for allogeneic SCT. In a retrospective analysis[39] by IBMTR for LBL patients, allogenic stem cell transplant patients were shown to have significantly lower relapse rates at 1 yr (32% vs 46%) and 5 yrs (34% vs 56%) compared to patients undergoing autologous transplant. However there was no significant difference in 5-yrs lymphoma-free survival or OS because of higher toxicity and early treatment related mortality (TRM) in allogenic transplant group. The relapse rate is higher after autologous transplantation and therefore patients with high risk features (such as marrow involvement) and a matched sibling donor should be offered an allogeneic transplantation in first remission. Patients who relapse with T-ALL and are transplanted in CR2 have a poor prognosis and so the initial management decision is crucial.

Response Evaluation

CT scan of affected area and Bone marrow and CSF evaluation (if involved at diagnosis) must be evaluated after initial chemotherapy.

6.5 Peripheral T Cell and Anaplastic large cell lymphoma

The mature or peripheral T-cell neoplasms are a biologically and clinically heterogeneous group of rare disorders that result from clonal proliferation of mature post-thymic lymphocytes. Natural killer (NK) cells are closely related to T cells and neoplasms derived from these are therefore considered within the same group. The World Health Organisation (WHO) classification of haemopoietic malignancies has divided this group of disorders into those with predominantly leukaemic (disseminated) nodal, extra-nodal or cutaneous presentation. Within the WHO classification, these malignancies are differentiated on the basis not only of clinical features but also of morphology, immunophenotype and genetics.

Together, the mature T- and NK-cell neoplasms account for approximately 10-12% of all lymphoid malignancies. There is geographical variation in the frequency of the different subtypes. The mature T-cell and NK-cell neoplasms usually affect adults and most of the entities described are more commonly reported in males than in females. The median age at diagnosis for the group as a whole is 61 years with a range of 17-90 years. Although some, such as T-cell large granulocyte leukaemia (T-LGL) and early stage mycosis fungoides (MF) may follow a relatively benign protracted course, others have an aggressive clinical behavior and poor prognosis. Excluding anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and indolent MF, which have a good outcome, 5 year survival for other nodal and extranodal T-cell lymphomas is about 30%. Most patients present with unfavourable international prognostic index (IPI) scores (>3) and poor performance status (PS). The similarity between progression free survival (PFS) and overall survival (OS) is an indication of the poor response to second line therapies..

Presentation

Extranodal presentation is common in PTCL[40] and this often contributes to a delay in diagnosis. When compared to aggressive B-cell lymphomas, patients tend to present with more advanced disease, a poorer performance status and an increased incidence of B-symptoms. Para-neoplastic features are well described including eosinophilia, haemophagocytic syndrome[41,42] and autoimmune phenomena. The latter are particularly seen in AITL.

Angioimmunoblastic T-Cell Lymphoma

Pathology

The lymph node architecture is partially effaced, and regressed follicles are often present. The paracortex is diffusely infiltrated by a polymorphous population of medium-sized lymphocytes, usually with clear to pale cytoplasm and distinct cell membranes. The lymphocytes show minimal cytological atypia, and this form of lymphoma may be difficult to distinguish from atypical T-zone hyperplasia. The abnormal lymphoid cells are admixed with small, reactive lymphocytes, eosinophils, plasma cells and histiocytes. There is marked proliferation of high endothelial venules and follicular dendritic cell meshworks are often increased. Increased numbers of B immunoblasts are usually present in the paracortex.

Immunophenotype

The infiltrates are composed of mature T-cells, usually with an admixture of CD4 and CD8 cells, with CD4 cells usually outnumbering CD8 cells. Follicular dendritic cells (CD21+) are prominent. The neoplastic T-cells may aberrantly express CD10.

Genetics

T-cell receptor genes are rearranged in 75% cases. Immunoglobulin gene rearrangement is present in 20-30% cases, correlating with clonally expanded EBV+ B cells. Gene expression studies confirm that the neoplastic cells are CD4+ TFH type.

Anaplastic Large Cell Lymphoma

Pathology

Pathological appearance is variable. LN / tissue architecture may be partly effaced and the disease typically grows within node sinuses. Morphology is variable, ranging from small cell neoplasms to cases with large anaplastic nuclei. All cases contain cells with eccentric reniform nuclei known as "hallmark cells" although the proportion of these cells present is variable. Morphologic variants include lympho-histiocytic, small cell, and Hodgkin-like patterns.

Immunophenotype

Cells are CD30+ve with cell membrane and Golgi region pattern. Most cases are EMA positive. CD2, CD4, CD5 are positive in 70% of cases. Most cases express T cytotoxic associated antigens including TIA-1, perforin and granzyme B. CD3, CD8, CD15 are negative in most cases. ALK protein is positive, most cases demonstrating both nuclear and cytoplasmic expression. Variant expression patterns, cytoplasmic, nuclear and membranous, exist.

Genetics

Around 90% cases show clonal T cell receptor gene rearrangements. Various ALK translocations are described: the most common, accounting for >80% of cases, is the t(2;5)(p23;p35) translocation involving the ALK gene and the nucleophosmin gene on 5q25 resulting in nuclear and cytoplasmic ALK protein expression. Variant translocations involving ALK and partner genes on chromosomes 1,2,3,17,19,22,X occur and are associated with variable protein expression patterns.

Staging

Staging is as for all lymphomas. The data suggest that most T-cell lymphomas are FDG-avid although with variable intensity. PET may be more useful at detecting residual disease at the end of treatment or during follow-up but may lack specificity and requires biopsy confirmation.

Prognosis

The International Prognostic Index (IPI) is well validated and in wide use for the assignment of B-lineage lymphoma patients to risk categories. It appears that the T-cell lymphomas can also be stratified effectively using the IPI although the greater proportion of cases are in the intermediate or high IPI groups which limits its usefulness. The ITLP demonstrated that the IPI was not helpful for enteropathy-associated T-cell lymphoma (EATL) and extra-nasal NK/TCL, since for these subtypes even a low IPI score was associated with a poor prognosis. An attempt to produce a more T-cell specific IPI identified four risk factors (age, LDH, bone marrow involvement and performance status) from which they defined four risk groups with 0, 1, 2 or >3 of these factors. Five year overall survivals for these groups were respectively: 62%, 53%, 33% and 18%.[43]

Treatment

From treatment point of view aggressive T cell non Hodgkin lymphoma is devided in to two groups. ALK positive ALCL; and PTCL-NOS & others.

The International Prognostic Index has predictive value in ALCL but ALK positivity is the most important prognostic factor. Treatment with an anthracycline-based chemotherapy regimen (eg, CHOP) results in five-year overall survival (OS) rates for patients with ALK positive ALCL from 70 to 93 percent. In comparison, patients with ALK negative ALCL have five-year OS rates after the same treatment regimens of 15 to 49 percent.

Patients with limited stage anaplastic large cell lymphoma and no adverse prognostic features by IPI should be treated with 3-4 cycles of CHOP chemotherapy and involved field radiotherapy. All other patients should receive 6-8 cycles of CHOP chemotherapy. ALK-neg ALCL should be treated as for PTCL-NOS.

The conventional chemotherapy regimens used to treat aggressive NHL (e.g. CHOP) have produced disappointing results in PTCL-NOS when compared to its B-cell counterpart or ALK-pos ALCL. This poor outcome for PTCL seems to be a combination of problems at all stages of the disease with lower initial response rates and a higher proportion of resistance and early death as well as a greater tendency to relapse after CR, mainly within the first 1-2 years. Unfortunately CHOP remains the most commonly used first line treatment despite the fact that it has never been established as the preferred or most effective treatment for non-ALK-pos PTCLs. Currently, however, there is insufficient data to recommend an alternative and trials are badly needed to explore new regimens. Outside a trial, a number of agents show promise, particularly gemcitabine[44] and praletrexate[45] but the data are insufficient to recommend routine use. Consideration should be given to consolidation with auto-HSCT[46].

In angio-immunoblastic T cell lymphoma, the timing and selection of therapy depend on clinical presentation and prognostic features. Patients requiring therapy should be entered into available clinical trials where possible. Outside a clinical trial, CHOP or FC would be considered as standard therapies. Consolidation radiation therapy is largely reserved for use in patients with localized (stage I or II) PTCL.

Autologous HCT is generally offered in addition to radiation for patients initially presenting with localized disease and an intermediate or high IPI. Autologous HCT, without radiation therapy, is offered to those who had extensive disease at the time of diagnosis as consolidation.

6.6 NK/T-Cell Lymphoma

NK/T cell lymphoma, nasal type is a predominantly extranodal lymphoma characterised by a broad morphologic spectrum. The lymphoma typically presents as a locally destructive proliferative lesion. The disease is most common in Asia, Mexico, Central and South America. Males predominate and the median age of presentation is 50 to 55 years. These lymphomas have also been described in immunosuppressed patients following organ transplantation.

Clinical Presentation

The commonest site is the nasal cavity. Identical neoplasms may be seen in other extranodal sites, including the nasopharynx, palate, skin, soft tissue, gastrointestinal tract and testis. Patients typically present with facial swelling and or mid-line facial destruction and the disease has an aggressive course. It is localised (stage I and II) in 80% at presentation but may disseminate to the skin, gastrointestinal tract, orbit, CNS or testis[47].

Pathology

This lymphoma is described as an angiocentric and angiodestructive, proliferative lesion. Fibrinoid changes, coagulative necrosis and apoptotic bodies are common. There is a broad spectrum of tumour cell morphology. Cells may be small, medium, large or anaplastic. They may have irregular nuclei which may be elongated, and nucleoli are generally inconspicuous. Mitotic figures are easily found. There may be a prominent inflammatory infiltrate.

Phenotype

The most common phenotype is CD2+, CD3-, CD56+, CD7-, Granzyme +. Other T and NK cell antigens are usually negative, including CD4, CD5, CD8, CD16 and CD57.

Genetics

T-Cell receptor and immunoglobulin genes are in germline configuration in the majority of cases, although T-cell receptor gene rearrangement may be detected. EBV genome is detected in tumour tissue using in situ hybridization for EBV-encoded RNA.

Staging

As for other aggressive lymphomas.

Investigations

As for other high grade lymphomas but should include in addition: a CT scan and MRI of nasal sinuses and brain. Lumbar puncture with cytology for malignant cells should also be performed.

Prognostic Factors / Index

The prognosis is variable, with some patients achieving complete responses to treatment, and others dying of progressive, disseminated disease. Extranodal involvement in nasal disease or disease occurring outside the nasal cavity, high Ki-67 staining and EBV DNA titer >6.1 X 10^7 copies /ml is very aggressive and associated with a short survival.

Treatment

Localised disease is treated[48] with intensive radiation therapy which results in a complete remission in two-thirds of patients although local relapse occurs in 50% and 25% of patients and progress to disseminated disease. Concurrent[49] or sequential chemoradiation is better approach.

For late stage disease (stages III and IV) combined modality therapy with radiation and chemotherapy and CNS prophylaxis is recommended. Recent literature suggests SMILE Chemotherapy Protocol[49,50] to be effective in relapsed NK-T cell NHL.

Response Evaluation and Follow Up

As for other aggressive lymphomas.

CHAPTER 7

SPECIAL PROBLEMS IN HIGH GRADE LYMPHOMAS

7.1 HIV-associated lymphoma

Lymphomas are an important complication of HIV infection and are a significant cause of morbidity and mortality. Most of these are aggressive B-cell lymphomas and are histologically heterogeneous. The common HIV-associated lymphomas are diffuse large B-cell lymphoma (DLBCL), which includes primary CNS lymphoma (PCNSL), and Burkitt lymphoma (BL), whereas primary effusion lymphoma (PEL), plasmablastic lymphoma (PBL) and classic Hodgkin lymphoma (HL) are far less frequent. Since the introduction of combination anti retroviral therapy (HAART), HIV-associated lymphomas have fallen in incidence and improved in outcome, in large part because of better control of HIV replication and improved immune function.

Workup

The diagnostic workup of HIV-associated lymphoma is not different from the non-HIV-associated lymphomas.

All patients with HIV-associated lymphoma regardless of histology should have a lumber puncture to rule out CNS involvement.

Baseline CD4 counts and HIV viral load should be obtained.

The role of PET in HIV-associated lymphomas is very poorly studied at this point of time because interpretation can be confounded by inflammatory reactions associated with HIV infection.

Treatment

Early introduction of HAART therapy is associated with superior outcomes. The addition of rituximab to CHOP has been associated with improved CR rates with manageable toxicities.

Patient should receive HAART and growth factor support along with full-dose chemotherapy. In patients with persistently low CD4 counts (<100/mcl), rituximab should be omitted to reduce the risk of serious infections. CNS prophylaxis can be considered for all patients or selected patients.

Treatment options for HIV-associated Burkitt lymphoma include CODOX-M/ IVAC, dose -adjusted EPOCH, or hyper-CVAD with or without rituximab. DLBCL should be treated CHOP+/- R or dose –adjusted EPOCH. Most cases of primary effusion lymphoma (PEL) are CD20-negative; the addition of rituximab to CHOP is not indicated. Plasmablastic lymphoma (PBL) can be treated with regimens recommended for Burkitt lymphoma. High-dose methotrexate or RT can be considered for patients with primary CNC lymphoma (PCNSL).

7.2 Primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL)

Primary central nervous system lymphoma (PCNSL) is usually an aggressive form of non-Hodgkin's lymphoma (NHL) arising in and confined to the brain, spinal cord, and leptomeninges. The intraocular

manifestation of PCNSL, which typically occurs in the retina, vitreous humour and, rarely, optic nerve, is termed "primary intraocular lymphoma" (PIOL). PIOL is a variant of PCNSL that can appear prior to, concurrent with, or subsequent to the cerebral disease. Although relatively rare, the incidence of both PCNSL and PIOL seems to be increasing. Over the last three decades survival has improved, mainly because of the introduction of methotrexate (MTX)-based combination chemotherapy. Long-term treatment-related neurological toxicity, however, remains a major problem. The role of consolidation radiotherapy is controversial.

The incidence of PCNSL has trebled over the last 30 years and, in the USA, is now 4.8 per million population per year. This disease accounts for approximately 5% of all primary brain tumours. Most series show a slight male preponderance of PCNSL, with most patients aged 60 years or more. The increase in the incidence of PCNSL cannot be explained solely by improved diagnostic technology because the incidence of other cerebral tumours has not shown a similar increase. Neither can it be explained by the human immunodeficiency virus (HIV) epidemic since the trend is also observed in populations with a low prevalence of HIV, and it far outpaces the increase seen in other HIV-related malignancies, such as Kaposi's sarcoma. Nevertheless, within the HIV+ population, NHL is the second most common malignancy, and previously PCNSL accounted for 20% of such cases. Prior to the advent of highly active anti-retroviral treatment, it was estimated that individuals with HIV infection were 3600 times more likely to develop PCNSL than the general population. Post-HAART the incidence has fallen dramatically.

Diagnosis

Unless clinically contra-indicated, such as in a patient with very poor performance status, diagnosis of PCNSL should always be confirmed histologically by image guided biopsy. Steroids are to be avoided pre surgery if at all possible. Biopsy samples for PCNSL and PIOL should be examined in centres with ready access to suitably qualified neurosurgery, neuropathology, ocular pathology and haematopathology specialists, and access to relevant immunocytochemical and molecular techniques.

In about 90% of cases, PCNSL can be sub-typed as a diffuse large B-cell lymphoma (DLBCL), according to the WHO Lymphoma Classification. The remainders are a mixture of Burkitt's lymphoma, T-cell rich B-cell lymphoma, peripheral T-cell lymphoma and rarely 'low-grade' B-cell lymphoma[51]. Leucocyte common antigen (CD45) is useful in distinguishing PCNSL from high-grade glioma and metastatic carcinoma.

Staging

Staging should include measurement of serum LDH; CT scanning of chest, abdomen and pelvis; testicular ultrasonography in elderly males; lumbar puncture for CSF protein/glucose quantification, cytology, flow cytometric analysis and immunoglobulin gene rearrangement studies and examination of the anterior chamber of the eye, vitreous and ocular fundus. Bone marrow involvement is rare but examination is advised to confirm that intracerebral disease is primary rather than metastatic. Intraocular lesions should be biopsied, and HIV infection should be confirmed or excluded in all patients.

Prognosis

A prognostic score should be calculated based upon age >60 years, performance status >1, raised LDH, raised CSF protein and involvement of deep brain matter (grade C, level IV)[52]. Baseline neuropsychological tests should be carried out before treatment and repeated during and after treatment. Patients and relatives should be warned of the risk of neurocognitive deterioration when consent for treatment is being obtained.

Treatment

All patients should be offered chemotherapy as first line treatment if they are sufficiently fit. Chemotherapy should consist of a regimen that includes HD Methotrexate (3-5 doses) of 3gm/m^2 delivered over a maximum of 2-3 hours at intervals of not more than 2-3 weeks. The efficacy of HD-Methotrexate may be improved by using it in combination with other CNS-penetrating chemotherapeutic agents such as cytarabine but such treatment should be based on established protocols[53-58].

Consolidation WBRT, 45 Gray in 25 fractions, should be considered in patients who achieve CR with MTX-based chemotherapy. In patients under 60 years of age, WBRT should be offered to patients unless there is a significant neurocognitive deficit following chemotherapy. In patients aged 60 years or over, neurocognitive side-effects are more likely to outweigh potential benefits.

There is no evidence supporting a role for intrathecal chemotherapy as an adjunct to high-dose intravenous MTX in patients with PCNSL[58]. Rituximab administered via the intrathecal or intraventricular route should not be used in the routine treatment of PCNSL except in a clinical trial.

Dexamethasone is the treatment of choice for short-term palliation but should be avoided before biopsy. Whole brain radiotherapy can provide effective palliation but should not be used as first-line therapy in patients who are sufficiently fit to receive chemotherapy.

There is no role for CHOP-like chemotherapy in the treatment of PCNSL

Relapsed or refractory disease should be treated with salvage radiotherapy in patients who have not previously received WBRT. Dexamethasone should be considered for short-term palliation. Alternative chemotherapeutic regimens such as temozolomide[59] or high-dose chemotherapy with autologous stem cell transplantation[60] show promise but require further evaluation in clinical trials.

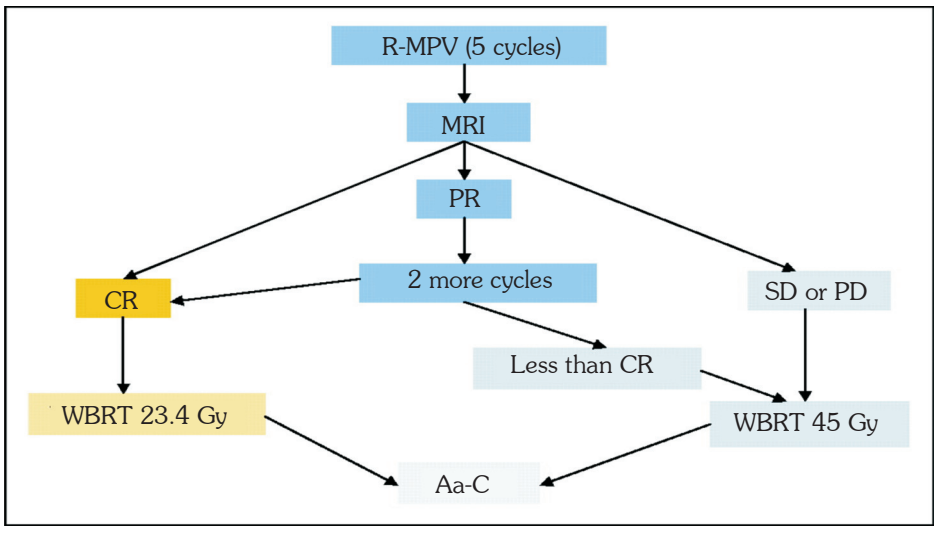
Concurrent intraocular and CNS lymphoma should be treated with systemic HD-Methotrexate based chemotherapy followed by radiation to both globes. Isolated intraocular disease should be treated in the same way. Intravitreal Methotrexate is an effective treatment option for patients with recurrent disease confined to the eyes.

Timely referral to rehabilitation and supportive care services is imperative and is dependent on rapid, comprehensive communication between medical and rehabilitation team.

Table 1: IPCG guidelines for baseline evaluation[61]			
Pathology	**Clinical**	**Laboratory**	**Imaging**
Report by histopathologist with expertise in neuropathology, ocular pathology and/or haematopathology and access to specialist neuropathology, ocular pathology and/or haematopathology	Complete medical and neurological examination	HIV serology	Contrast-enhanced cranial MRI scan (CT if MRI contraindicated)
Immunophenotyping and where appropriate molecular testing	Dilated eye examination, including slit lamp examination and fundoscopy	Vitreous biopsy +/- chorioretinal biopsy, immunohistochemistry, IgH-PCR1, serum LDH level	CT of chest, abdomen and pelvis
	Record prognostic factors (age, performance status)	CSF cytology, flow cytometry, IgH-PCR	Bone marrow aspirate and trephine biopsy
	Serial evaluation of cognitive function	24-hour urine collection for creatinine clearance if HD-MTX planned	Testicular ultrasound in elderly males

Table 2: IPCG response criteria[61]				
Response	**Brain imaging**	**Glucocorticoid dose**	**Eye examination**	**CSF cytology**
CR	No enhancing disease	None	Normal	Negative
uCR	No enhancing disease Minimal enhancing disease	Any Any	Normal Minor RPE abnormality	Negative Negative
PR	50% decrease in enhancement No enhancing disease	NA NA	Minor RPE abnormality or normal Decrease in vitreous cells or retinal infiltrate	Negative Persistent or suggestive of disease
PD	25% increase in enhancement Any new site of disease	NA	Recurrent or new disease	Recurrent or positive
SD	All scenarios not covered by responses above			

RPE- Retinal pigment epithelium



Reference [59]

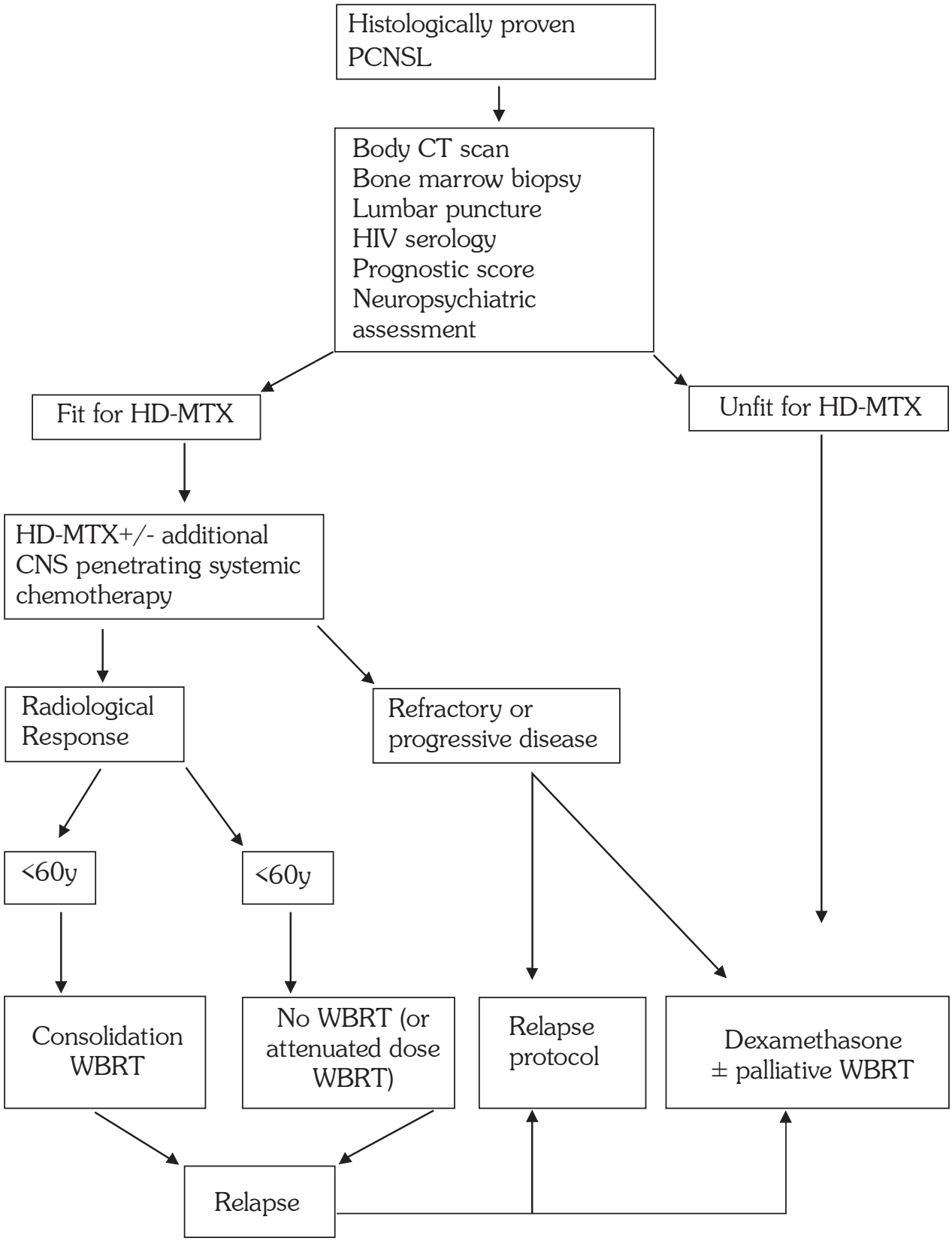


Figure 1. Suggested treatment algorithm for first-line therapy

7.3 Primary Testicular Lymphoma (PTL)

Introduction: NHL of the testis (PTL) is an uncommon and rare disease that represents 1% to 2% of all NHLs and about 5% of all testicular neoplasms[62-64]. However, it represents the most frequent testicular cancer in men older than 60 years of age (85% of PTLs are diagnosed in men > 60 years of age).

Clinical presentation: The most common clinical presentation is a unilateral painless scrotal swelling[65,66] and systemic symptoms are usually present only in advanced stages (25% - 41% of patients). Less frequently, abdominal pain and ascites can be seen in patients with enlarged retroperitoneal lymph nodes. Bilateral testicular involvement (up to 35% of patients) may be synchronous at diagnosis or, more frequently, asynchronous during the course of the disease. PTL has a propensity to disseminate systemically to several extranodal sites including the contralateral testis, central nervous system (6% - 16%), skin (0% - 35%), Waldeyer's ring (5%), lung, pleura and soft tissue[65-67]. Involvement of these sites may occur either concurrently or subsequently during the course of the disease[68,69].

Pathology: Around 80-90% of PTLs are diffuse large cell lymphomas with B-cell phenotype (DLBCL)[63] and 10-20% of cases are Burkitt's or Burkitt's-like (mainly in HIV-positive patients) and rarely T-cell, lymphoblastic or follicular lymphomas have been reported. Immunohistochemistry is useful to differentiate from germ cell tumours.

Diagnosis and Staging: Orchidectomy is the method of choice for pathological diagnosis and it also removes the main tumour mass allowing a good local tumour control. Staging procedures are similar to those applied in nodal lymphomas. Additionally CSF examination, Waldeyer's ring and G-I tract evaluation, screening ultrasound of the contralateral testis and a thorough clinical skin examination should be performed.

Prognostic factors: AAdverse prognostic indicators for PTL as reported by some studies are as follows: older age, poor performance status, systemic symptoms, tumor burden higher than 9 cm, spermatic cord involvement, high LDH levels, high histologic grade, vascular invasion, higher degree of sclerosis, and advanced stage of disease[63,70-72]. In a large study by of the International Extranodal Lymphoma Study Group (IELSG), clinical features significantly associated with a longer OS in multivariate analysis were: low/low-intermediate IPI score, no B symptoms, anthracycline-containing regimens, prophylactic scrotal radiotherapy[62].

Prognosis: PTL behaves aggressively with a poor outcome. The two largest series of PTL reported so far are a retrospective survey by the IELSG (373 patients)[62] and a US SEER database (769 patients)[70]: both studies showed a continuous risk of relapse and disease-related deaths, even 10 years after diagnosis. Most relapses occur within the first two years of follow-up. In most series, relapses occurred in extranodal sites such as CNS, skin, lung, pleura, soft tissue, Waldeyer's ring[62,71]. One of the peculiar features of PTL is a contralateral testis relapse occurring in 5-35% of the patients. Moreover CNS relapses are definitely more common than in other aggressive lymphomas and they have been reported up to 30% of the patients within 1-2 years from diagnosis[62]. Disseminated lymphomas involving the testis (stage IV disease) show a very aggressive behavior with more than 90% relapse rate and a 5-year survival of 20% - 25%[62,71].

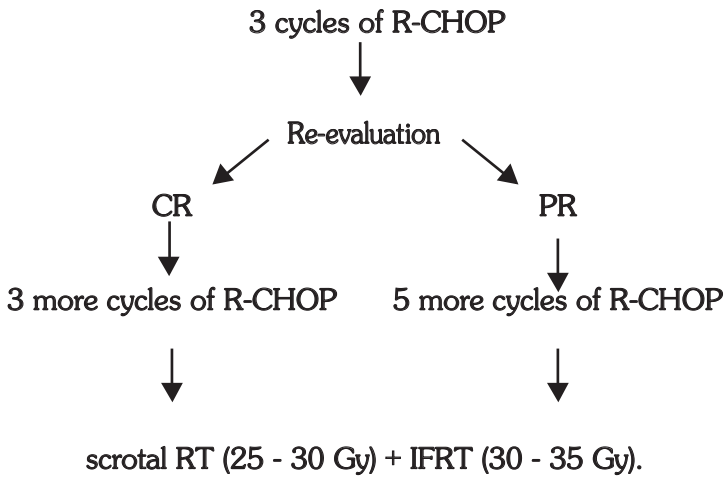
Management of limited stage disease (stage IE - IIE) (based on IELSG-10 study)[72]

Standard management guidelines for patients with PTL have not been yet established[63].

PPTL patients with limited disease should be managed with primary orchidectomy followed by R-CHOP treatment, CNS prophylaxis (intrathecal chemotherapy+/-high-dose Methotrexate or high-dose Cytarabine) and prophylactic scrotal radiotherapy. In patients with stage-IIE disease, irradiation of involved lymph nodes is advisable.

Stage IE: A total of 6 cycles of R-CHOP followed by scrotal RT (25 – 30 Gy, including RT to the contralateral testis), along with four doses of intrathecal Methotrexate on days 1, 8, 15, and 22 (starting from day 1 of Cycle I R-CHOP).

Stage IIE:



Four doses of intrathecal Methotrexate on days 1,8,15,22 (starting from day 1 of Cycle I R-CHOP).

Management of advanced stage disease (stage III - IV): PTL patients with stage III or IV should be treated according to the guidelines for the treatment of advanced stage nodal DLBCL[73,74]. The usual therapeutic option for these patients is conventional-dose anthracycline-containing chemotherapy with Rituximab along-with prophylactic scrotal radiotherapy and intrathecal chemotherapy[73,74]. The addition of intermediate-high dose methotrexate might improve CNS prophylaxis, especially in the younger patients but this has never been formally demonstrated[75]. High-dose chemotherapy followed by stem cell transplantation may be an investigational option.

Management of relapsed or refractory disease: Management guidelines should be the same as for other aggressive NHLs. Therapeutic decision should be strongly influenced by age, performance status and clinical condition of the patient. High-dose chemotherapy followed by autologous stem cell rescue is the treatment of choice in patients less than 60 years with chemo-sensitive relapse.

7.4 Primary gastrointestinal lymphoma

Gastrointestinal tract is the most common extranodal site involved by lymphoma accounting for 5%-20% of all cases. Primary gastrointestinal lymphoma, however, is very rare, constituting only about 1%-4% of all gastrointestinal malignancies. Gastrointestinal lymphoma is usually secondary to the widespread nodal diseases.

Pathology

Although lymphoma can arise from any region of the gastrointestinal tract, the most commonly involved sites are the stomach followed by small intestine and ileocecal region.

Histopathologically, almost 90% of the primary gastrointestinal lymphomas are of B cell lineage with very few T-cell lymphomas and Hodgkin lymphoma. Certain histological subtypes have been noted to have a relative predilection site as mucosa-associated lymphoid tissue (MALT) lymphoma in stomach, mantle cell lymphoma (MCL) in terminal ileum, jejunum and colon, as well as enteropathy-associated

T-cell lymphoma (EATL) in jejunum, and follicular lymphoma (FL) in duodenum. Multifocality, however, has been noticed particularly in MALT lymphoma and FL.

Risk factors

Certain risk factors have been implicated in the pathogenesis of gastrointestinal lymphoma including Helicobacter pylori (H. pylori) infection, human immunodeficiency virus (HIV), celiac disease, Campylobacter jejuni (C. jejuni), Epstein-Barr virus (EBV), hepatitis B virus (HBV), human T-cell lymphotropic virus-1 (HTLV-1), inflammatory bowel disease and immunosuppression.

Dawson's criteria for primary gastrointestinal lymphoma

Dawson's criteria are used for labeling primary gastrointestinal lymphoma, that include

(1) Absence of peripheral lymphadenopathy at the time of presentation;

(2) lack of enlarged mediastinal lymph nodes;

(3) Normal total and differential white blood cell count;

(4) Predominance of bowel lesion at the time of laparotomy with only LNs obviously affected in the immediate vicinity;

(5) No lymphomatous involvement of liver and spleen.

Staging and investigations

Ann Arbor staging with Musshoff modification is commonly employed to stage gastrointestinal lymphoma and the IPI has been used to define the prognostic subgroups.

The different procedures employed for the pre-treatment staging include endoscopic ultrasound (EUS), endoscopic biopsies, computed tomography (CT), magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) or molecular markers. All patients with GI lymphoma should have a careful ENT examination because of the 20% risk of associated involvement at that site

Treatment

Treatment of gastro-intestinal lymphoma is according to histological subtype. Previously, resection of GI lymphoma to prevent hemorrhage or perforation was recommended, however, earlier diagnosis and current management techniques seem to have reduced this risk. Thus, resection of GI lymphoma is no longer recommended, unless necessary to establish a definite diagnosis or to control the complications of hemorrhage or perforation.

CHAPTER

8 MANAGEMENT OF RELAPSED LYMPHOMAS

Aggressive or High Grade NHLs are associated with responses in approximately half the patients treated with combination chemotherapy including anthracyclines, alkylating agents, vinca alkaloids and steroids. Despite these initial responses, about one third of patients are either refractory to, or relapse after standard therapy. Patients with higher IPI scores are more likely to respond poorly to therapy and have worse progression free survival than others. Attempts to predict poor response have been made using gene-expression profiling and early PET imaging i.e. after 1-3 cycles of chemotherapy, however, clear guidelines are not available for the same.

The majority of relapses occur during the first two years after completion of treatment. Relapsed NHL may be classified as early or late (occurring >5 years after therapy). In a study of patients who relapsed later, it was seen that localized stage, favorable IPI score, and extranodal involvement at diagnosis was more common in this subgroup[76]. In another study, early relapse was defined as that occurring within 12 months of therapy[77].

Evaluation of suspected relapse

Regular follow up is essential for all patients who have been treated with high dose chemotherapy. Each visit should involve a complete physical examination with special attention paid to examination of the sites of nodal and extra-nodal involvement. Any change in clinical status should prompt an immediate investigation directed towards identifying relapsed disease.

- Histopathological examination is mandatory in the evaluation of relapsed disease. Although most DLBCL relapses have the same histology, occasional indolent relapses have also been observed[78].
- In addition to involved nodal sites, a careful search for extranodal involvement must be carried out.
- Complete restaging with imaging, routine laboratory investigations and a bone marrow aspiration and trephine biopsy must be done in all cases.
- In patients with relapses involving the neuroaxis, directed imaging and a lumbar puncture must be done.
- The IPI should be determined again at the time of relapse as it remains predictive of outcome..

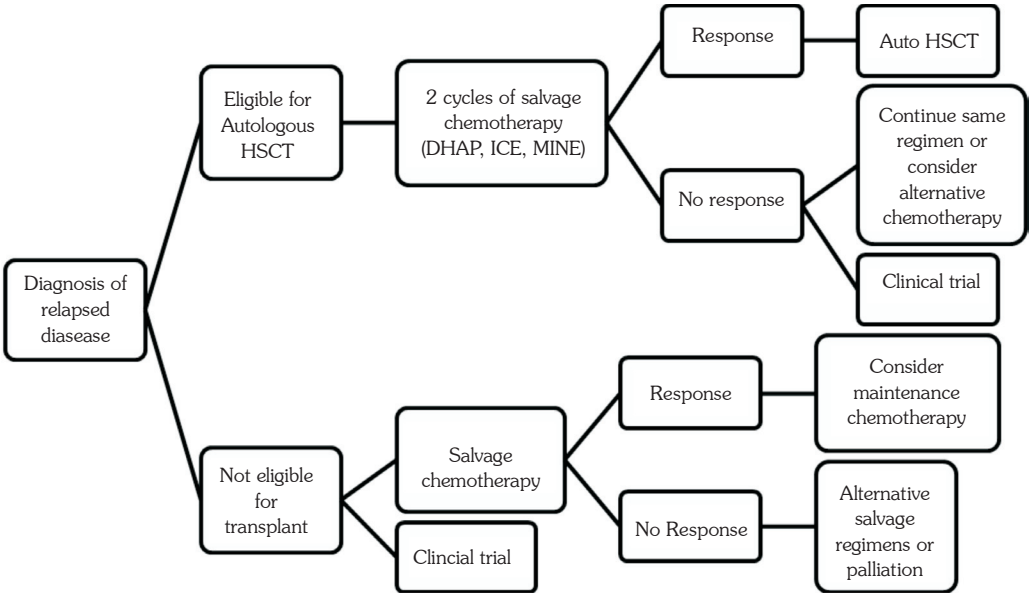
Management strategy

The choice of chemotherapy regimen depends on whether the patient is a transplant candidate or not. Autologous stem cell transplantation after high dose chemotherapy has been shown to be effective in the treatment of relapsed NHL.[79] Therefore, the first step in the planning of therapy is the assessment of whether or not the patient is eligible for autologous HSCT.

Although no clear guidelines exist regarding the eligibility criteria for autologous HSCT, common exclusion criteria include advanced age (typically >60- 65 years), presence of significant organ dysfunction

(pulmonary, cardiac, hepatic or renal), poor ECOG performance status and the unavailability of adequate financial and social support for post transplant care.

A suggested algorithm is as follows



8.1 Salvage Chemotherapy Regimens

Many chemotherapy regimens exist for the treatment of relapsed NHL. Patients who are suitable for autologous transplantation should not receive highly myelotoxic regimens for fear of depleting stem cell reserve.

Chemotherapy regimens for potential candidates for stem cell therapy

Platinum compound based regimens have been associated with good responses and lower levels of myelotoxicity and are widely used for salvage chemotherapy in potential transplant candidates. These include:-

- **DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab**[80] In the initial study of the DHAP regimen, complete response was seen in 34% patients whereas partial response was seen in about 23% after two cycles of chemotherapy. Hematologic toxicity is universal with 57% patients requiring transfusion of blood products. Severe (grade 3/4) nonhematologic side effects include infection (24%) and nephrotoxicity (6%).
- **ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab**[81] Out of 122 patients studied, 37% attained a complete remission and 27% attained a partial remission with an overall response rate of 64% after two cycles. Hematologic toxicity is universal with significant rates of neutropenic fever (30%) if growth factors are not used. Other side effects are generally mild and include nausea, vomiting, diarrhea, nephrotoxicity, and electrolyte disturbances.
- **GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab**[82] After two cycles of chemotherapy, the overall response rate was 49% with 16% showing complete remission and 33% partial remission. Hematologic toxicity is universal. Febrile neutropenia is seen in approximately 15% patients.
- **GemOx (gemcitabine, oxaliplatin) ± rituximab**[83] A response rate of 43% with 39% showing complete response was observed using this regimen. It is important to note that these patients received six to

eight cycles of chemotherapy. Side effects include severe hematologic toxicity in approximately 50% patients and neuropathy, which can be severe.

- **ICE (ifosfamide, carboplatin, etoposide) ± rituximab**[84] Out of 222 patients studied, an overall response rate of 71.6% was seen, with a complete response rate of 28.4% and a partial response rate of 43.2%. The addition of rituximab improved the response rate by approximately 10%. Hematologic toxicity is universal in this regimen with 35% patients requiring transfusion of blood products. Severe (grade 3/4) nonhematologic side effects include infection (23%) and nephrotoxicity (1%).
- **MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab**[85] Response rates of 57% with 33% complete remission have been reported in early studies. Long term disease free survival rates up to 65% at 10 years were also seen. Hematological toxicity is universal with 18% patients developing febrile neutropenia. Neurotoxicity and mucositis were also observed.

Use of additional anthracyclines must be accompanied by careful monitoring of the cardiac status. Dexrazoxane may be added for additional cardioprotection. Disease status should be evaluated with imaging studies and clinical assessment after two to three cycles, following which autologous HSCT should be carried out.

Chemotherapy regimens in patients who are not candidates for stem cell therapy

- Clinical trial
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab[86] Bleomycin may also be added to this regimen. In the study quoted, 40% patients achieved a complete response and 32% achieved a partial response, providing an overall response rate of 72%.
- DA-EPOCH ± rituximab[87] Out of 125 assessable patients, 24% achieved complete responses and 50% achieved partial responses. Significant haematological toxicity is present. Even though the regimen contains doxorubicin, no cardiac deaths were observed in the trial. Also, 88% patients had already received at least four of the agents used in EPOCH as prior chemptherapy.
- GDP ± rituximab
- GemOx ± rituximab
- Lenalidomide ± rituximab[88] Lenalidomide may be effective in relapsed cases of NHL by virtue of its unique mechanism of action and its anti-angiogenic and immunomodulatory effects. Side effects are primarily haematological. In the study quoted, patients received 25 mg lenalidomide orally for 21 days out of 28 for a total period of 52 weeks. An objective response rate of 35% was observed in 49 treated patients, including a 12% rate of complete response/unconfirmed complete response.

8.2 Hematopoietic Stem Cell Transplantation

In the absence of stem cell therapy, salvage chemotherapy regimens can only provide transient remissions in patients with relapsed disease. Autologous hematopoietic stem cell transplantation (HSCT) after high dose chemotherapy in chemotherapy sensitive disease is associated with better event free and progression free survival than salvage chemotherapy alone[79]. The rate of event-free survival was 46% in patients who received stem cell therapy versus 12% in the group receiving chemotherapy without transplantation, and the rate of overall survival was 53% and 32%, respectively.

The response to initial salvage chemotherapy is an important predictor of response after HSCT. Patients with less chemosensitive disease usually have less durable responses and are more likely to

relapse after HSCT[89]. Patients having PET positivity prior to transplantation are shown to have worse outcomes than patients with PET negative disease[90].

Conditioning regimens used in autologous HSCT differ according to the center and local experience.

Commonly used conditioning regimens include

- BCNU, cyclophosphamide, cytosine arabinoside and melphalan (BEAM)[91]
- Busulfan and cyclophosphamide (Bu-Cy)
- Melphalan, busulfan, and total body irradiation (TBI)[92]
- Cyclophosphamide (with or without etoposide) plus TBI[93]
- Bendamustine, etoposide, cytarabine, melphalan (BeEAM)[94]
- Thiotepa, busulfan, and cyclophosphamide (TBC)[95]
- Lomustine (CCNU), cytarabine (Ara-C), cyclophosphamide, etoposide (LACE)[96]

All conditioning regimens are highly toxic and cause fatal myeloablation unless stem cell rescue is implemented. Peripheral blood stem cell collection is usually preferred over bone marrow collection due to quicker engraftment and a potential for less contamination of the infused cells with malignant cells. Stem cell mobilisation strategies also vary from center to center.

Allogenic Stem Cell Transplantation

Allogeneic HSCT is associated with higher transplant related mortality and morbidity but not significantly different rates of event free survival as compared to autologous HSCT. Due to complications associated with graft versus host disease and infections, the treatment-associated mortality in these studies has ranged from 20% to 50%[97]. Allogeneic HSCT may be considered in younger patients with stem cell mobilisation failure or relapse after autologous HSCT that are able to tolerate high dose chemotherapy a second time. Alternative donor sources, reduced intensity conditioning and tandem transplants are still experimental and no guidelines exist for the same.

CHAPTER 9

FOLLOW UP

Most patients with High Grade Lymphoma can be cured with the treatments described in this section. Most cured patients experience minimal long-term toxicity from the treatments; however, certain predictable and unpredictable late effects may occur and require preventive measures and/or recognition and treatment.

Patients should be followed up every 3 to 4 months for the first 2 years, followed by 6 monthly for the next 3 years and then annually. The following format shall be followed:

1. Accurate history,
2. Careful physical examination,
3. Hematological investigation,
4. Documentation of side effects: late effects of treatment,
5. Documentation of second primary,
6. Documentation of any other findings.

Most cured patients experience minimal long-term toxicity from the treatments, however, certain predictable and occasional rare and unpredictable late effects may occur and require preventive measures and/or early recognition and treatment.

The following late effects of Lymphoma or its treatment should be considered when patients are reviewed in follow-up.

Risk/Problem	Incidence/Response
Relapse	20-50% of patients relapse depending on histologic subtype, stage and bulk of presentation. Careful attention should be directed to lymph node sites, especially if previously involved with disease.
Dental Caries	Neck or oropharyngeal irradiation may cause decreased salivation. Patients should have careful dental follow-up and should make their dentist aware of the previous irradiation.
Hypothyroidism	After external beam thyroid irradiation to doses sufficient to cure NHL, at least 50% of patients will eventually become hypothyroid. All patients whose TSH level becomes elevated should be treated with life long thyroxine replacement in doses sufficient to suppress TSH levels to low normal.

Infertility	Multi-agent chemotherapy and direct or scatter radiation to gonadal tissue may cause infertility, amenorrhea or premature menopause All patients should be advised that they may or may not be fertile after treatment. In general, after treatment, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer.
Secondary Neoplasms	Although quite uncommon, certain neoplasms occur with increased frequency in patients who have been treated for lymphoma. These include acute myelogenous leukemia, thyroid, breast, lung and upper gastrointestinal carcinoma and melanoma and cervical carcinoma-in-situ. It is appropriate to screen for these neoplasms for the rest of the patient's life because they may have a lengthy induction period.

The following minimum follow-up tests and examinations should be performed on all patients after treatment for malignant lymphoma. Visits should be every 3-4 months for 2 year, then every 6 months for 3 years, then annually. Female patients should be strongly encouraged to perform careful breast examination on a regular basis.

Interval	Test
Every visit	Lymph node, abdominal, thyroid, and skin examination. CBC, alkaline phosphatase, LDH, chest radiograph (if original disease was in the thorax)
Once every 12 to 18 months	Chest Radiograph TSH level (if the thyroid gland was irradiated) Mammography for women after age 40 Pap's Smear

Surveillence PET scan has no role in the patient follow up as of date and must be used judiciously

CHAPTER

10 SUPPORTIVE CARE

10.1 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an oncological emergency. The incidence of TLS in all patients with malignancies ranges from 5% to 20%. It is a series of life threatening complications after the lysis of tumor cells in patients undergoing treatment for malignancies. Because of the significant morbidity associated with TLS, early recognition in patients with lymphoma is critical for good outcomes.

Mild consequences of TLS may delay treatment, and severe consequence may result in death; thus, identification of risk factors and prevention are of paramount importance. Risk factors for the development of TLS include tumor type (Burkitt's lymphoma, lymphoblastic lymphoma, acute lymphoblastic leukemia), large tumor load, LDH two times upper normal limit, WBC count 25,000 cmm/L, pre-existing renal failure or oliguria, uric acid level and effective or prompt cytoreductive therapy. The incidence of TLS in a study of high-grade NHL was about 42%, but only a few (6%) present with obvious clinical features[98].

Although TLS can occur as a result of chemotherapy and radiotherapy, there have been only 7 reports of TLS occurring after rituximab treatment. TLS presenting in absence of chemotherapy is a rare occurrence. The etiology of the spontaneous TLS is not well understood, which complicates the diagnosis. Spontaneous TLS is rare but presents added risks to the patient because of the potential for delayed diagnosis and no benefit of pretreatment. Diagnosis may be further delayed because this may be the first symptom of underlying malignancy.

The main patho-physiology mechanism of TLS is the massive lysis of tumor cells and rapid release of intracellular toxic metabolites (potassium, phosphate, and uric acid) that overwhelm the metabolic and excretory capacity of the liver and kidneys. TLS can be divided into laboratory tumor lysis syndrome (LTLS) and clinical tumor lysis syndrome[99]. The criteria for LTLS include uric acid >8.0 mg/dl, potassium 6.0 mmol/L, phosphorous >6.5 mg/dl for children and >4.5 mg/dl for adults or each parameter increased by 25%, and calcium <7.0 mg/dl or decreased by 25%. The occurrence of at least 2 laboratory abnormalities within 3 to 7 days after cytotoxic therapy is considered evidence of LTLS. Clinical tumor lysis syndrome is diagnosed when one of the following symptoms occur when LTLS criteria are met: renal impairment, arrhythmia, sudden death or seizures.

TLS-induced renal impairment is cause by the deposition of uric acid crystals in the renal tubules. The traditional treatment of TLS includes oral administration of allopurinol (300–600 mg/d) until the uric acid level returns to normal. When hyperkalemia occurs, calcium gluconate (100–200 mg/kg) and insulin in 10% glucose can be administered intravenously to promote the entry of potassium into the cells. For improvement of renal blood flow, a low dose of dopamine can be given. Diuresis may be performed to increase urine volume and the excretion of metabolites. Hypocalcemia is difficult to correct and may be caused by hypomagnesemia. Therefore, magnesium sulfate (25–100 mg/kg) may be administered intravenously. Of note, all treatments should be performed in combination with hydration (2 to 3 L/m^2 daily) to achieve a urine output of at least 80 to 100 ml/m^2 per hour is recommended.

When acidosis is difficult to correct and concomitant renal failure is present hemodialysis is recommended. Hemodialysis is an important strategy in the treatment of TLS. Hemodialysis should be considered when continuous hyperkalemia, significant metabolic acidosis, volume overload, non-response to diuretics or obvious symptoms of uremia are present. When significant hyperphosphatemia (6 mg/dL) and hypocalcemia are present, prophylactic hemodialysis is recommended even in the absence of uremia.

In recent years, several studies have indicated that recombinant urate oxidases, such as rasburicase, are more effective than allopurinol in reducing the level of uric acid and can be used for the prevention of purine crystal-induced renal failure. Rasburicase catalyzes the conversion of uric acid to the highly water-soluble compound allantoin, which is easily eliminated in urine. This reduces plasma uric acid and prevents the development of uric acid nephritis. In a randomized controlled trial, children with hematologic malignancies (acute lymphoblastic leukemia or type III/IV NHL) were stratified and then randomly assigned to receive rasburicase or allopurinol. Children treated with rasburicase had significantly lower uric acid levels and smaller areas under curve compared with patients treated with allopurinol. Rasburicase is contraindicated for patients with methemoglobinemia, glucose-6-phosphate dehydrogenase deficiency and other metabolic diseases that can cause hemolytic anemia. For these individuals, oral allopurinol treatment, hydration and urinary alkalinization are recommended. In addition, controversy remains regarding the benefits of urine alkalization in patients receiving urate oxidases.

In summary, TLS is one of the causes of death in patients with malignant lymphomas. The clinical manifestations of TLS are not typical, and its diagnosis is based on laboratory examination. Although uncommon, TLS can occur with rituximab administration. It may be possible to prevent TLS or reduce TLS-related mortality by identifying patients at high risk for TLS and making preparations (such as hospitalization, hydration, starting allopurinol, and urinary alkalinization) before starting treatment. Close monitoring of renal parameters in initial part of treatment is strongly recommended. .

10.2 Viral Reactivation

Introduction: For cancer patients who have chronic hepatitis B virus infection, there is a high rate of hepatic complications during cytotoxic chemotherapy, and this has mainly been attributable to HBV reactivation. The condition is manifested with abnormal liver function tests confirmed by raised levels of serum HBV DNA. The clinical spectrum ranges from symptomatic hepatitis to fatal hepatic failure. The incidence of HBV reactivation in hepatitis B surface antigen (HBsAg) seropositive cancer patients undergoing cytotoxic chemotherapy has been reported to be 20% or higher.

Risk factors for reactivation: With the increasing incidence of neoplastic diseases and the more widespread use of cytotoxic chemotherapy, the occurrence of HBV reactivation is likely to increase further. Identified risk factors include detectable pre-chemotherapy HBV DNA load (using real-time PCR measurement), the use of steroids, a diagnosis of lymphoma or breast cancer, the use of anthracyclines, male sex, younger age, and HBeAg positivity.

Diagnostic criteria: Hepatitis B virus reactivation is characterized by two main parameters: rising serum HBV DNA levels followed by rising ALT. There are no clear cut diagnostic criteria for HBV reactivation. One proposed definition was a sudden rise in serum ALT more than five times the upper limit of normal or more than three times baseline level, whichever was higher. Other definitions include a 10-fold rise in viral load or HBV DNA levels exceeding approximately 6log10 copies/ml Essentially, measuring viral load and ALT are the key to diagnosing and monitoring reactivation. Reactivation most frequently follows cessation of chemotherapy, but may occur during chemotherapy. The reported interval ranges from 4 to 36 weeks (median, 16 weeks) from initiation of chemotherapy. Since many patients are asymptomatic, regular monitoring of ALT and HBV DNA is essential.

Prevention of HBV This is superior to intervention at the time of reactivation. Preventive measures start with proper screening for HBV markers before initiation of chemotherapy followed by active immunisation of all HBV susceptible patients (also including bone-marrow and stem cell donors). Candidate patients with overt or occult HBV must be identified and protected against HBV by an anti-viral agent.

Screening of patients prior to initiation of chemotherapy: All patients diagnosed with lymphoma should be screened for HBV infection. Initial screening is based on serological tests for anti-HBc antibodies, HBsAg and anti-HBs antibodies. Seronegative patients should be actively vaccinated against HBV. HBsAg positive patients are considered carriers and should be protected pre-emptively against HBV reactivation by an anti-viral agent before initiation of chemotherapy. All HBsAg positive patients should be further tested for HBeAg, anti-HBe, HBV DNA and anti-HBc IgM.

Intervention upon diagnosis of hepatitis B reactivation: When HBV reactivation is diagnosed, prompt anti-viral therapy is vital. Aggressive supportive therapy should be instituted along with cessation of chemotherapy and withdrawal of potential hepatotoxic agents. Patients should be monitored closely in consultation with an expert hepatologist. Currently, lamivudine is the primary agent for treatment for HBV reactivation in the setting of immune suppression. Mortality may be as high as 40% despite lamivudine if severe hepatic injury is present.

Pre-emptive anti-viral therapy against hepatitis B reactivation: Several reports have demonstrated the benefit of pre-emptive treatment with lamivudine in patients at risk of HBV reactivation. The optimal timing for beginning pre-emptive anti-viral therapy has not been established but it is preferable to begin pre-emptive treatment 2–3 weeks prior to chemotherapy, and no later than the first day of chemotherapy. The optimal duration of prophylactic anti-viral therapy in patients at risk is unclear. Despite the absence of well controlled trials, treatment must be maintained for at least 6 months and preferably 12 months after completion of chemotherapy. Extended treatment for >12 months after chemotherapy may be advisable in patients who initially had high serum HBV DNA levels, at the discretion of the treating physician. At present, reports on lamivudine resistance in patients with HBV reactivation are scarce. Newer and more potent anti-viral agents will enable effective protection despite the emergence of escape mutants.

In conclusion, ssurveillance for HBV status is an integral part of the care of the lymphoma patient. By implementing good medical practice, virtually all patients should be prevented from contracting or reactivating HBV, in view of the potentially serious consequences of this infection.

10.3 Fertility Issues in High grade NHL

Since the introduction of aggressive chemotherapy, alone and in combination with irradiation, long-lasting remissions and cures have been obtained in patients with high-grade NHL. Although a more aggressive therapy may result in an improved remission rate, it is usually associated with amenorhoea and infertility in 33–75% patients.

Therapy-induced gonadal toxicity has become an issue of clinical concern to these patients for several reasons. First, many patients are young adults concerned about their reproductive potential after therapy. Second, cure rates have gone beyond 40-50% in high grade NHL, thus exposing a large group of long-term survivors to this potential toxicity. Third, gonadal injury may not only result in reduced fertility but also effect gonadal steroid synthesis, which may be associated with cardiovascular, sexual, and emotional disorders. In contrast to the knowledge on late toxicity following therapy for HD, only a few data are known about gonadal toxicity of patients with NHL. According to one recent report, no effects on gonadal function were found following standard-dose VACOP-B or MACOP-B combination chemotherapy for NHL.

The frequency of gonadal dysfunctions is markedly lower in patients treated for NHL than in patients treated for HD, approximately half of whom will be affected by long-term gonadal toxicity. Gonadal toxicity following cancer therapy in female patients mainly involves endocrine gonadal functions and in men primarily spermatogenesis. They may be detrimental even to resting and immature oocytes and possibly damage pre-granulosa cells of primordial follicles. Particularly radiotherapy and the use of agents such as mechlorethamine, cyclophosphamide, or procarbazine have been held responsible for the gonadal damage in patients with lymphoma.

The available data suggest that 90% of females treated with CHOP do preserve ovarian function, possibly due to a relatively low cumulative dose of cyclophosphamide, totaling 4.5 to 6 g/m2. Pelvic radiation is extremely deleterious to the germinal epithelium of the testes and ovaries, leading to impaired fertility or sterility, even after very low exposures (4 to 6 Gy). In males, Leydig cell function is rarely affected with usually normal pubertal development, testicular volume and sexual function. On the other hand, sterility is a big issue in male survivors. Oligospermia may already exist at the time of diagnosis in 30 to 40% patients but, despite of this, sperm cryopreservation should always be considered before initiating therapy in pubertal boys. However, late (10 to 15 years later) recovery of fertility has also been reported, hence, caution is always required when discussing this prognosis with the patients. In women, the deleterious effects of pelvic irradiation can be prevented by the surgical transfer of the ovaries to the midline (oophoropexy).

The POF (Primary ovarian failure) rate was reported to be as high as 60–90% in the application of regimens with higher doses of alkylating agents, used as conditioning for stem cell transplantation hormonal disorders were more common in autologous or allogeneic bone marrow transplantation, 58 or 78% respectively, compared with 23% in a cohort of patients who had intensive consolidation chemotherapy. Apparently, POF correlates with age and cumulative dose of the alkylating agent. Time schedule may also play a role. Effects on the ovaries are dependent on the age of the woman at the time of therapy, with younger girls having the higher probability of maintaining regular menses after treatment.

Normal pregnancies can occur after oophoropexy and pelvic irradiation without increased risk of fetal wastage or spontaneous abortion. No increase in birth defects could be observed in offspring of survivors when compared with those of sibling controls. Sperm banking before treatment commences is available for males but unfortunately cryopreservation of ovarian tissue is not yet established for females.

The use of GnRH analogue in combination with chemotherapy may possibly have a protective effect on oocytes in some female patients exposed to conventional dose chemotherapy however; its efficiency may be limited in patients undergoing high-dose chemotherapy with stem cell rescue.

10.4 NHL during Pregnancy

NHL in pregnancy is a rare event. MRI can replace staging CT but is not advisable in the first trimester. Patients with aggressive NHL usually have stage II-IV disease and present at a median of 23 weeks of gestation. Prolonged delay in treatment is likely to have serious consequences for the patient. If the patient is diagnosed in the first trimester, termination prior to the commencement of chemotherapy should be offered. For those patients diagnosed after 32 weeks, it may be possible to delay treatment until safe delivery of the child is possible. For those patients that fit into neither of the above categories, a decision will have to be made as to when treatment should start.

Preferred treatment for high grade NHL is R-CHOP. There are case reports of Rituximab being given uneventfully in pregnancy but its license does not cover this group of patients. Anthracyclines and steroids

have been used in the second and third trimester of pregnancy with one group reporting normal child development with a follow-up of several months to 11 years after anthracycline therapy. Ectrodactylia was reported in 2 of 3 cases exposed to cyclophosphamide in utero. One case report describes cardiac abnormalities. The risks appear higher in the first trimester. Vincristine has been linked with abnormalities in 2 children, both born to mothers receiving combination chemotherapy. In 14 infants born to mothers treated only with Vincristine, no abnormalities were reported. It is thus difficult to calculate the risk to the foetus and ultimately the decision on when to treat must rest with the patient. For patients diagnosed with indolent NHL during pregnancy, there is usually very little requirement to treat at the time of diagnosis. If treatment becomes necessary, the same considerations as above need to be given.

10.5 Immunization

Patients who have lymphoma should receive certain immunizations to help boost or maintain their immunity. However, immunizations using live organisms are theoretically dangerous and should be avoided unless advised by Hemato-oncologist, to have one (exception, Zostavax ®, see below). Patients who are currently receiving chemotherapy or radiation should wait until six months after treatment before receiving immunizations, except for influenza vaccine, which can be taken every year.

Type of Immunization	When Should it be Given?
Influenza vaccine	Every year in Sep-Oct
Pneumococcal vaccine	At the time of diagnosis, if the pneumococcal vaccine can be given at least 2 weeks before initiation of anti-lymphoid cancer treatment. If that is not possible, delay until at least 6 months after completion of all lymphoid cancer treatment and any other immunosuppressive treatment. Repeat again once 5 years later.
Tetanus/diphtheria	Every 10 years
Meningococcal Men-C-C and, 2 weeks later, Men-P-ACYW and Hemophilus influenza type b vaccine	If the spleen is to be or was removed or treated with radiation, give all 3 at least 2 weeks before splenectomy, if possible, or, if spleen already removed, give as soon as possible after splenectomy. Repeat Men-P-ACYW every 5 years.
Polio vaccine	Oral polio vaccine should never be taken by patients with lymphoid cancer. It has been replaced by inactivated polio vaccine, which is safe for patients with lymphoid cancer.
Measles (live virus) Mumps (live virus) Rubella (live virus) Yellow fever (live virus)	Never
Varicella (chicken pox) vaccine (Zostavax ® live attenuated virus)	At the time of diagnosis, Zostavax ® can be given at least 2 weeks before initiation of anti-lymphoid cancer treatment. If that is not possible, delay until at least 6 months after completion of all lymphoid cancer treatment and any other immunosuppressive treatment.

CHAPTER

11 RADIOTHERAPY

Lymphomas in general are very sensitive to ionizing radiation. Radiation therapy (RT) has remained an integral part in the combined modality treatment (CMT) of malignant lymphomas.

Currently most patients with localized DLBCL and a significant proportion of patients with disseminated disease with bulky nodes are treated with CMT approach using multiagent chemotherapy and RT.

The optimal radiation dose after chemotherapy has not been determined. A retrospective study from Florida recommended 30 Gy for patients with non-bulky tumour (<6 cm) if complete remission was achieved by chemotherapy, otherwise 40-/45 Gy was recommended after chemotherapy

11.1 Radiation Therapy Field Size/Treatment Volume

The optimal treatment volume or field size for RT of localized NHL is also a matter of some controversy. Conclusions regarding appropriate field size are extrapolated from information regarding patterns of failure.

For DLBCL, the pattern of failure after CMT is usually disseminated disease, with a small percentage with local failure. After chemotherapy alone, more local failure occurs.

In view of the patterns of failure data, IFRT was established as the most appropriate field. In clinical practice the entire involved nodal region is included in the RT field, e.g. patients presenting with nodal disease in the neck unilaterally, would receive RT to the entire neck nodes on that side. It is a regular practice to restrict IFRT to the postchemotherapy volume in situations where excessive dose to normal tissue might result, such as with primary DLBCL of the mediastinum. Similarly for large nodal masses in the retroperitoneal region or pelvic cavity that have responded to chemotherapy and reduced in size, the postchemotherapy volume is usually included in the transverse dimensions without compromising on the vertical extent of the nodal chain in order to reduce the possibility of nephrotoxicity and urinary bladder and bowel toxicity.

In patients with large residual masses in proximity to critical organs, a shrinking field technique can be used where the radiation field size is reduced as the treatment progresses / tumor shrinks and thereby restricting the RT dose to the nearby critical structures.

Newer RT techniques like 3 dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) can significantly reduce radiation doses to surrounding normal tissues.

CHAPTER

12 RESEARCH ISSUES

1. Developing set of minimum markers to diagnose sub types of lymphoma in Indian setting.
2. Adherence of clinicians to proposed guidelines of treatment.
3. Making national registries for rare sub types of lymphoma, eg bone lymphoma, primary CNS lymphoma or testicular lymphoma.
4. Determination of incidence and prevalence of lymphoma in various regions of India.
5. Developing consensus protocols for management of various subtypes of lymphoma.
6. Role of radiotherapy in management of lymphoma in today's era.

CHAPTER

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CHAPTER

14 APPENDIX

CHOP[16,100]
Cyclophophamide (Cytoxan) 750 mg/m^2 iv d1
Doxorubicin (Adriamycin) 50 mg/m^2 iv d1
Vincristine 1.4 mg/m2 (max 2 mg) iv d1
Prednisone 100 mg po qd d1-5
Q3w x 6-8 cycles

R-CHOP[16,100]
Rituximab (Rituxan) 375 mg/m^2 iv d1
Cyclophophamide (Cytoxan) 750 mg/m2 iv d1
Doxorubicin (Adriamycin) 50 mg/m^2 iv d1
Vincristine 1.4 mg/m2 (max 2 mg) iv d1
Prednisone 100 mg po qd d1-5
Q3w x 6-8 cycles

CEPP[101] (non-anthracycline-containing regimen)
Cyclophosphamide (Cytoxan) 600 mg/m^2 iv d1 and 8
Etoposide (VP-16) 70 mg/m^2/d iv d1-3
Procarbazine 60 mg/m^2/d po d1-10
Prednisone 60 mg/m^2/d po d1-10
Q4w x 6 cycles

ICE[102]
Ifosfamide 5000 mg/m2 mixed with Mesna 5000 mg/m^2 iv over 24 hrs d2
Carboplatin (Paraplatin) AUC 5 (max 800mg) iv d2
Etoposide (VP-16) 100 mg/m^2/d iv d1-3
Filgrastim (Neupogen) 5 ug/kg sc qd d5-12
Q2w x 3 cycles

RICE[103]
Rituximab (Rituxan) 375 mg/m^2 iv d1 q2w x 3 cycles
ICE regimen as above

EPOCH[89,104]
Etoposide (VP-16) 50 mg/m^2/d civi d1-4
Prednisone 60 mg/m^2/d po d1-5

Vincristine 0.4 mg/m^2/d civi d1-4
Doxorubicin (Adriamycin) 10 mg/m^2/d civi d1-4
Cyclophosphamide (Cytoxan) 750 mg/m^2 iv over 15 min d5
Bactrim DS 1 tablet po bid tiw
Filgrastim (Neupogen) 5 mcg/kg sc qd beginining on d6 till ANC > 10,000/uL
Q3w x 6-8 cycles

Dose-adjusted EPOCH[105]
Etoposide (VP-16) 50 mg/m^2/d civi d1-4
Prednisone 60 mg/m2/d po d1-5
Vincristine 0.4 mg/m2/d civi d1-4
Doxorubicin (Adriamycin) 10 mg/m^2/d civi d1-4
Cyclophosphamide (Cytoxan) 750 mg/m^2 iv over 15 min d5
Bactrim DS 1 tablet po bid tiw
Filgrastim (Neupogen) 5 mcg/kg sc qd beginining on d6 till ANC > 5,000/uL
Q3w x 6-8 cycles
Dose-adjustment paradigm based on twice weekly CBC (dose adjustment above starting doses apply to Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytoxan). Dose adjustment below starting dose apply to Cyclophosphamide.
If nadir ANC > 500/uL, 20% increase in Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytoxan) above last cycle
If nadir ANC < 500/uL on 1 or 2 measurements, same doses as last cycle
If nadir ANC < 500/uL on at least 3 measurements, or nadir platelet < 25,000/uL on 1 measurement, 20% decrease in Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytoxan) below last cycle

ESHAP[83]
Etoposide (VP-16) 40 mg/m^2/d iv over 1 hr d1-4
Methylprednisolone 500 mg/d iv over 15 min d1-5
Cisplatin (CDDP) 25 mg/m^2/d civi d1-4
Cytarabine (Ara-C) 2000 mg/m^2 iv over 2 hr d5
Q3-4w x 6-8 cycles

MINE[106,107]
Mesna 1330 mg/m2/d iv over 1 hr with ifosfamide d1-3, then 500 mg po 4 hrs after ifosfamide d1-3
Ifosfamide 1330 mg/m^2/d iv over 1 hr d1-3
Mitoxantrone (Novantrone) 8 mg/m^2 iv d1
Etoposide (VP-16) 65 mg/m^2/d iv over 1 hr d1-3
Q3w

DHAP[82]
Dexamethasone (Decadron) 40 mg po qd d1-4
Cisplatin (CDDP) 100 mg/m^2 iv over 24 hrs d1
Cytarabine (Ara-C) 2000 mg/m^2 iv q12 hrs for 2 doses d2
Q3-4w

R-GemOx[85,108]
Rituximab (Rituxan) 375 mg/m^2 iv d1
Gemcitabine (Gemzar) 1000 mg/m^2 iv d2
Oxaliplatin (Eloxatin) 100 mg/m^2 iv over 2 hrs d2
Q2-3w x 8 cycles

Burkitt's lymphoma
CODOX-M/IVAC[27] (for high risk patients: do not meet low risk below)
Cycle 1 and 3 (CODOX-M)
Cyclophosphamide (Cytoxan) 800 mg/m^2 iv d1
Cyclophosphamide (Cytoxan) 200 mg/m^2/d iv d2-5
Doxorubicin (Adriamycin) 40 mg/m^2 iv d1
Vincristine 1.5 mg/m2 iv d1, 8 for cycle 1 and d1, 8, 15 for cycle 3
Methotrexate (MTX) 1200 mg/m^2 iv over 1 h d10, then 240 mg/m2 per hour civi for the next 23 hrs
Leucovorin 50 mg iv q6h begins 36 hrs from the start of MTX till MTX level < 0.05 uM
Filgrastim (Neupogen) begins 24 hrs from the start of Leucovorin till ANC > 1000/mL
CNS prophylaxis:
Intrathecal Cytarabine (Ara-C) 70 mg d1 and 3, Methotrexate (MTX) 12 mg d15
CNS treatment:
Cycle 1: Intrathecal Cytarabine (Ara-C) 70 mg d1, 3 and 5, Methotrexate (MTX) 12 mg d15 and 17
Cycle 3: Intrathecal Cytarabine (Ara-C) 70 mg d1 and 3, Methotrexate (MTX) 12 mg d15
Cycle 2 and 4 (IVAC)
Ifosfamide 1500 mg/m^2/d iv d1-5
Etoposide (VP-16) 60 mg/m^2/d iv d1-5
Cytarabine (Ara-C) 2000 mg/m^2 iv q12h d1 and 2 (total 4 doses)
Filgrastim (Neupogen) begins 24 hrs after completion of chemotherapy till ANC > 1000/mL
CNS prophylaxis:
Intrathecal Methotrexate (MTX) 12 mg d5
CNS treatment:
Cycle 2: Intrathecal Methotrexate (MTX) 12 mg d5, Cytarabine (Ara-C) 70 mg d7 and 9
Cycle 4: Intrathecal Methotrexate (MTX) 12 mg d5

Radiotherapy for CNS disease and testicular involvement

Modified CODOX-M[27] (for low risk patients: single extraabdominal mass or completely resected abdominal mass and normal serum LDH)

Cyclophosphamide (Cytoxan) 800 mg/m^2 iv d1
Cyclophosphamide (Cytoxan) 200 mg/m^2/d iv d2-5
Doxorubicin (Adriamycin) 40 mg/m2 iv d1
Vincristine 1.5 mg/m2 iv d1, 8
Methotrexate (MTX) 1200 mg/m^2 iv over 1 h d10, then 240 mg/m^2 per hour civi for the next 23 hrs
Leucovorin 50 mg iv q6h begins 36 hrs from the start of MTX till MTX level < 0.05 uM
Filgrastim (Neupogen) begins 24 hrs from the start of Leucovorin till ANC > 1000/mL

CNS prophylaxis:
Intrathecal Cytarabine (Ara-C) 70 mg d1, Methotrexate (MTX) 12 mg d3
Total of 3 cycles

CALGB 9251[33,109]
Cycle 1
Cyclophosphamide (Cytoxan) 200 mg/m^2/d iv d1-5
Prednisone 60 mg/m^2/d po d1-7
Cycle 2, 4, 6
Ifosfamide 800 mg/m^2/d iv over 1 hr d1-5
Mesna 200 mg/m2 iv at 0, 4 and 8 hrs after ifosfamide d1-5
Methotrexate (MTX) 150 mg/m^2 iv over 30 minutes d1, followed by 1350 mg/m^2 civi over 23.5 hrs
Leucovorin 50 mg/m^2 iv 36 hrs after start of MTX, followed by 15 mg/m2 iv q6h till MTX level < 0.05 uM
Vincristine 2 mg iv d1
Cytarabine (Ara-c) 150 mg/m^2/d civi d 4 and 5
Etoposide (VP-16) 80 mg/m^2/d iv over 1 hr d 4 and 5
Dexamethasone (Decadron) 10 mg/m^2/d po d1-5
Cycle 3, 5, 7
Cyclophosphamide (Cytoxan) 200 mg/m^2/d iv d1-5
Methotrexate (MTX) 150 mg/m^2 iv over 30 minutes d1, followed by 1350 mg/m^2 civi over 23.5 hrs
Leucovorin 50 mg/m2 iv 36 hrs after start of MTX, followed by 15 mg/m^2 iv q6h till MTX level < 0.05 uM
Vincristine 2 mg iv d1
Doxorubicin (Adriamycin) 25 mg/m^2/d iv bolus d 4 and 5
Dexamethasone (Decadron) 10 mg/m^2/d po d1-5
Intrathecal (cycle 2-7)
Methotrexate (MTX) 15 mg d1
Cytarabine (Ara-c) 40 mg d1
Hydrocortisone 50 mg d1
Brain radiation 24 Gy post chemotherapy if bone marrow involvement
Start cycle 2 right after cycle 1, cycle 2-7 are given q3w

Lymphoblastic Lymphoma
Hyper-CVAD/MTX-Ara-C[110]
Cycle 1,3,5,7 (3-4 wks/cycle)
Cyclophosphamide (Cytoxan) 300 mg/m2 iv over 2 hrs q12 hrs x 6 doses d1-3
Mesna 600 mg/m^2/d civi d1-3 to start 1 h before cyclophosphamide till 12 hrs after completion of cyclophosphamide
Vincristine 2 mg iv d4, 11
Doxorubicin (Adriamycin) 50 mg/m^2 iv over 24 hrs (over 48 hrs if LVEF < 50%) d4
Dexamethasone (Decadron) 40 mg po or iv qd d1-4 and d11-14
Cycle 2,4,6,8 (3-4 wks/cycle)
Methotrexate (MTX) 200 mg/m^2 iv over 2 hrs followed by 800 mg/m2 civi over 22 hrs d1
Cytarabine (Ara-C) 3 g/m2 (1 g/m2 for patients over 60 years old) iv over 2 hrs q12 hrs x 4 doses d2-3

Leucovorin 50 mg iv q6 hrs starting 12 hrs after completion of MTX till MTX level < 0.05 uM
Intrathecal chemotherapy
Prophylaxis
Methotrexate (MTX) 12 mg d2 of each cycle for a total of 3-4 treatments
Cytarabine (Ara-C) 100 mg d8 of each cycle for a total of 3-4 treatments
Therapeutic
Intrathecal chemotherapy twice a week (Methotrexate (MTX) 12 mg and Cytarabine (Ara-C) 100 mg respectively) till no more cancer cells in CSF, then decrease intrathecal chemotherapy to once a week x 4, followed by Methotrexate (MTX) 12 mg d2, Cytarabine (Ara-C) 100 mg d8 for the remaining chemotherapy cycles

Cranial radiotherapy 24-30 Gy if cranial nerve palsies

CALGB 9111[111]
Cycle 1 (4 wks)
Cyclophosphamide (Cytoxan) 1200 mg/m^2 iv d1
Doxorubicin (Adriamycin) 45 mg/m^2/d iv d1, 2, 3
Vincristine 2 mg iv d1, 8, 15, 22
Prednisone 60 mg/m^2 po or iv qd d1-21
L-Asparaginase 6000 IU/m2 sc or im d5, 8, 11, 15, 18, 22
Reduce doses if patients older than 60:
Cyclophosphamide (Cytoxan) 800 mg/m^2 iv d1
Doxorubicin (Adriamycin) 30 mg/m^2/d iv d1, 2, 3
Prednisone 60 mg/m^2 po qd d1-7
Filgrastim (Neupogen) 5 mcg/kg sc qd d4 till ANC > 1000/uL
Cycle 2 (4 wks,repeat once)
Cyclophosphamide (Cytoxan) 1000 mg/m^2 iv d1
6-Mercaptopurine (6-MP) 60 mg/m^2/d po d1-14
Cytarabine (Ara-C) 75 mg/m^2/d sc d1-4 and 8-11
Vincristine 2 mg iv d15, 22
L-Asparaginase 6000 IU/m2 sc or im d15, 18, 22, 25
Intrathecal Methotrexate (MTX) 15 mg d1
Filgrastim (Neupogen) 5 mcg/kg sc qd d2 till ANC > 5000/uL
Cycle 3 (12 wks)
6-Mercaptopurine (6-MP) 60 mg/m^2/d po d1-70
Methotrexate (MTX) 20 mg/m^2 po d36, 43, 50, 57, 64
Intrathecal Methotrexate (MTX) 15 mg d1, 8, 15, 22, 29
Brain radiation 24 Gy d1-12
Cycel 4 (8 wks)
Doxorubicin (Adriamycin) 30 mg/m^2/d iv d1, 8, 15
Vincristine 2 mg iv d1, 8, 15
Dexamethasone (Decadron) 10 mg/m^2/d po d1-14
Cyclophosphamide (Cytoxan) 1000 mg/m^2 iv d29
6-Thioguanine 60 mg/m2/d po d29-42
Cytarabine (Ara-C) 75 mg/m^2/d sc d29-32 and 36-39
Cycle 5 (16 months)

Vincristine 2 mg iv d1 qm
Prednisone 60 mg/m^2/d d1-5 qm
Methotrexate (MTX) 20 mg/m^2/d po d1, 8, 15, 22
6-Mercaptopurine (6-MP) 60 mg/m^2/d po d1-28

SMILE Chemotherapy Protocol
Methotrexate 2 g/m^2 IV (6 hours) on Day 1
Leucovorin 15 mg X 4 IV or PO on Day 2, 3, 4
Ifosfamide 1,500 mg/m^2 IV on Day 2, 3, 4
Mesna 300 mg/m^2 X 3 IV on Day 2, 3, 4
Dexamethasone 40 mg/d IV or PO on Day 2, 3, 4
Etoposide 100 mg/m^2 IV on Day 2, 3, 4
L-asparaginase (**Escherichia coli**) 6,000 U/m^2 IV on Day 8, 10, 12, 14, 16, 18, 20
G-CSF SC or IV Day 6 to WBC >5,000/µL
NOTE. Cycles were repeated every 28 days. Two courses were planned as the protocol treatment.

Primary CNS lymphoma
High dose Methotrexate[112]
Methotrexate (MTX) 8 g/m^2 iv over 4 hrs q2w till CR or up to 8 cycles, followed by 8 g/m2 iv qm x 11 months
MPV + RT + Ara-C[113,114]
Methotrexate (MTX) 3.5 g/m^2 iv over 2 hours d1
Leucovorin 10 mg q6h x 12 doses starting 24 hours after MTX infusion
Vincristine 1.4 mg/m^2 (max 2.8 mg) iv d1
Procarbazine 100 mg/m^2 po qd d1-7 cycles 1, 3, 5 only
Q2w x 5 cycles
Intra-ommaya Methotrexate (MTX) 12 mg on alternate weeks after systemic MTX
Leucovorin 10 mg q6h x 8 doses starting 24 hours after intra-ommaya MTX
3-5 weeks after MPV, whole-brain radiotherapy (WBRT) 1.8 Gy/d x 25 days to a total of 45 Gy for patients younger than 60 years
3 weeks after WBRT, consolidation Cytarabine (Ara-C) 3 g/m^2/d iv over 3 hours for 2 days. A second cycle of Cytarabine (Ara-C) is given 1 month later
R-MPV + RT + Ara-C[59]
Rituximab (Rituxan) 500 mg/m^2 iv over 5 hours d1 of each cycle
Methotrexate (MTX) 3.5 g/m^2 iv over 2 hours d2 of each cycle
Leucovorin 20-25 mg q6h starting 24 hours after MTX infusion for 72 hours or until serum MTX level < 1 x 10^{-8} mg/dL. Increase leucovorin to 40 mg q4h if MTX level > 1 x 10^{-5} mg/dL at 48 hours or > 1 x 10^{-8} mg/dL at 72 hours
Vincristine 1.4 mg/m2 (max 2.8 mg) iv d2 of each cycle
Procarbazine 100 mg/m2 po qd d1-7 of odd-numbered cycles only
Filgrastim (Neupogen) 5 mcg/kg/d sc for 3 to 5 days starting 24 hours after the last dose of procarbazine during odd-numbered cycles, and starting 96 hours after MTX infusion or when MTX levels < 1 x 10^{-8} mg/dL during even-numbered cycles
If positive CSF cytology: intra-ommaya Methotrexate (MTX) 12 mg between days 5 and 12 of each cycle
Q2w x 5 cycles

After 5 cycles of R-MPV:
If CR, whole-brain radiotherapy (WBRT) 1.8 Gy/d for 13 days to a total of 23.4 Gy beginning 3-5 weeks after the completion of R-MPV
If PR, 2 more additional cycles of R-MPV. If CR after 7 cycles of R-MPV, WBRT 1.8 Gy/d x 13 days to a total of 23.4 Gy beginning 3-5 weeks after the completion of R-MPV. If persistent disease after 7 cycles of R-MPV, WBRT 1.8 Gy/d x 25 days to a total of 45 Gy beginning 3-5 weeks after the completion of R-MPV
If stable disease or progressive disease after 5 cycles of R-MPV, WBRT 1.8 Gy/d x 25 days to a total of 45 Gy beginning 3-5 weeks after the completion of R-MPV
3 weeks after completion of WBRT, consolidation Cytarabine (Ara-C) 3 g/m2/d (max 6 g) iv over 3 hours for 2 days
Filgrastim (Neupogen) 5 mcg/kg/d sc for 10 days starting 48 hours after completion of Ara-C
A second cycle of Cytarabine (Ara-C) is given 1 month later
Temozolomide
Temozolomide (Temodar) 150 mg/m2/d po d1-5 q4w

R-MPV + RT + Ara-C[59]
Rituximab 500 mg/m^2 iv over 5 hours d1 of each cycle
Methotrexate (MTX) 3.5 g/m^2 iv over 2 hours d2 of each cycle
Leucovorin 20-25 mg q6h starting 24 hours after MTX infusion for 72 hours or until serum MTX level < 1 x 10^{-8} mg/dL. Increase leucovorin to 40 mg q4h if MTX level > 1 x 10^{-5} mg/dL at 48 hours or > 1 x 10^{-8} mg/dL at 72 hours
Vincristine 1.4 mg/m^2 (max 2.8 mg) iv d2 of each cycle
Procarbazine 100 mg/m^2 po qd d1-7 of odd-numbered cycles only
Filgrastim 5 mcg/kg/d sc for 3 to 5 days starting 24 hours after the last dose of procarbazine during odd-numbered cycles, and starting 96 hours after MTX infusion or when MTX levels < 1 x 10^{-8} mg/dL during even-numbered cycles
If positive CSF cytology: intra-ommaya Methotrexate (MTX) 12 mg between days 5 and 12 of each cycle
Q2w x 5 cycles
After 5 cycles of R-MPV:
If CR, whole-brain radiotherapy (WBRT) 1.8 Gy/d for 13 days to a total of 23.4 Gy beginning 3-5 weeks after the completion of R-MPV
If PR, 2 more additional cycles of R-MPV.
If CR after 7 cycles of R-MPV, WBRT 1.8 Gy/d x 13 days to a total of 23.4 Gy beginning 3-5 weeks after the completion of R-MPV.
If persistent disease after 7 cycles of R-MPV, WBRT 1.8 Gy/d x 25 days to a total of 45 Gy beginning 3-5 weeks after the completion of R-MPV
If stable disease or progressive disease after 5 cycles of R-MPV, WBRT 1.8 Gy/d x 25 days to a total of 45 Gy beginning 3-5 weeks after the completion of R-MPV
3 weeks after completion of WBRT:
consolidation **Cytarabine** (Ara-C) 3 g/m^2/d (max 6 g) iv over 3 hours for 2 days
Filgrastim 5 mcg/kg/d sc for 10 days starting 48 hours after completion of Ara-C
A second cycle of Cytarabine (Ara-C) is given 1 month later
Detailed evidence regarding management of various subtypes of Non Hodgkin Lymphoma can be obtained from recent version of NCCN guidelines[115].

CHAPTER

15 ABBREVIATIONS

ABC	Activated B cell like
AFB	Acid-Fast Bacilli
AIDS	Acquired immune deficiency syndrome
AITL	Angioimmunoblastic T-Cell Lymphoma
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic lymphoma Kinase
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine aminotransferase
Ara-C	Arabinoferanosyl cytosine
ASCR	Autologus stem cell rescue
ASCT	Allogenic Stem Cell Transplant
AST	Aspartate aminotransferase
BCL	B Cell Lines
BCNU	Bis Chloroethyl Nitrosourea
BEAM	BCNU, Etoposide, Cytarabine, Melphelan
BeEAM	Bendamustine, Etoposide, Cytarabine Melphelan
BL	B Lymphocytes
BM	Bone Marrow
BMA	Bone Marrow Aspiration
Bu-Cy	Busulfan Cyclophosphamide
CBC	Complete Blood Count
CCNU	Chloroethyl Cyclohexylnitrosourea
CD	Cluster of Differentiation
CEPP	Cyclophosphamide, Etoposide, Prednisone, Procarbazine
CHOP	Cyclophosphamide/ Doxorubicin/ Vincristine/ Prednisone
CLL	Chronic lymphocytic Leukemia
CLPD	Chronic Lymphoproliferative Disorder
CME	Continuing Medical Education
CMT	Combined Modality Treatment
CNS	Central Nervous System
CODOX	Cyclophosphamide, Vincristine, Doxorubicin, High Dose Methotrexate
CR	Complete Remission
Cru	Complete Remission Unconfirmed
CRP	C-Reactive Protein
CRT	Chemoradiation
CSF	Cerebrospinal Fluid
CT	Computed Tomography

CVAD	Central Venous Access Device
CXR	Chest Xray
DA-EPOCH	Dose Adjusted- EPOCH
DCT	Direct Coombs Test
DHAP	Dexamethasone, High Dose ara- C, Platinol
DLBCL	Diffuse Large B-cell Lymphoma
DNA	Deoxy ribonucleic acid
EATL	Enteropathy Associated T-cell Lymphoma
EBV	Ebstein Barr virus
ECOG	Eastern cooperative oncology group
EDTA	Ethylene diamine tetraacetic acid
EMA	Epithelial membrane antigen
ENT	Ear, Nose, Throat
EPOCH	Etoposide, Prednisolone, Oncovin, Cyclophosphamide, Haloteatin
ER	Estrogen Receptor
ESHAP	Etoposide, Solumedrol, Ara C, Platinol
ESR	Erthyocyte Sedimentation Rate
FAB	French American British
FC	Flow Cytometric
FCM	Flow Cytometry
FDG-PET	Fluorodeoxyglucose Positron emission tomography
FISH	Fluoroscent in-situ hybridization
FL	Follicular Lymphoma
FLIPI	Filamin A Interacting Protein 1
FNA	Fine Needle Aspiration
FNAC	Fine Needle Aspiration Cytology
GC	Germinal Centre
GCB	Germinal Centre B-Cell
GDP	Gemcitabine, Dexamethasone, Cisplatin
GemOx	Gemcitabine Oxaliplatin
GI	Gastrointestinal
GIT	Gastrointestinal Tract
GMS	Gomori's Methanamine Silver
HAART	Highly Active Antiretroviral Treatment
H&E	Hematoxylin and Eosin
HBeAg	Extracellular form of HBcAg
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCT	Hematopoietic Cell Transplantation
HCV	Hepatitis C virus
HD	Hodgkins Disease
HD-MTX	High dose Methotrexate
HDT	High dose chemotherapy
HHV	Human Herpes virus
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HLN	Hematolymphoid neoplasm

HSCT	Homologous stem cell transplant
HTLV	Human T Lymphotropic Virus
IBMTR	International Bone Marrow Transplant Registry
ICE	Intracardiac Echocardiography
IELSG	International Extranodal Lymphoma Study Group
Ig	Immunoglobulin
IFRT	Involved Field Radiotherapy
IHC	Immunohistochemistry
IMRT	Intensity Modulated Radiotherapy
IPCG	International Primary CNS Lymphoma Collaborative Group
IPI	International Prognostic Index
IPT	Immunophenotyping
IRF	Interferon Regulatory Factor
ITLP	International T-cell Lymphoma Project
IVAC	Ifosphamide, Etoposide, Highdose Cytarabine
LACE	Life After Cancer Epidemiology
LBL	Lymphoblastic Lymphoma
LCA	Leukocyte Common Antigen
LDH	Lactate Dehydrogenase
LN	Lymphnode
LP	Lumbar Puncture
LTLS	Long Term Lapse Study
MALT	Mucosa Associated Lymphoid Tissue
MCL	Mantle Cell Lymphoma
MF	Mycosis Fungoides
MINE	Mesna, Ifosfamide, Novantrone, Etoposide
MIPI	Mantle Cell International Prognostic Score
MPO	Myeloperoxidase
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
MUGA	Multigate Radionucleotide Angiography
MUM-1	Multiple Myeloma Oncogene-1
NA	Not Applicable
NG	Not Given
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NLPHL	Nodular Lymphocyte Predominant Hodgkin's Lymphoma
NOS	Not Otherwise Specified
OS	Overall Survival
OT	Operation Theatre
PAS	Periodic Acid Schiff
PBL	Peripheral Blood Lymphocytes
PBS	Peripheral Blood Smear
PCNSL	Primary CNS Lymphoma
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PEL	Primary Effusion Lymphoma

PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography- Computed Tomography
PFS	Progression Free Survival
PICC	Peripherally Inserted Central Catheter
PIOL	Primary Intraocular Lymphoma
POF	Primary Ovarian Failure
PR	Partial Remission
PS	Performance Status
PTCL	Peripheral T-Cell Lymphoma
PTL	Primary Thyroid Lymphoma
PTLD	Post Transplant Lymhoproliferative Disease
R-IPI	Revised International Prognostic Index
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
RT	Radiotherapy
RT-PCR	Real Time Polymerase Chain Reaction
SCT	Stem Cell Transplant
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SMZL	Splenic Marginal Zone Lymphoma
SOP	Standard Operating Procedures
SPD	Sum of the product of the greatest diameters
SWOG	Southwest Oncology Group
TBC	Thiotepa, Busulfan, Cyclophosphamide
TBI	Total Body Irradiation
TCL	T-Cell Leukemia
TCR	T-Cell Receptor
TdT	Terminal Deoxynucleotidyl Transferase
TFH	Follicular Helper CD4 T Cells
T-LGL	T-cell Large Granular Lymphocytic Leukemia
TLS	Tumor Lysis Syndrome
TRM	Treatment Related Mortality
TSH	Thyroid- Stimulating Hormone
Ttg	Tissue Transglutaminase
ULN	Upper Limit of Normal
USG	Ultrasound
WBC	White Blood Cell
WBRT	Whole Brain Radiation Therapy
WHO	World Health Organization