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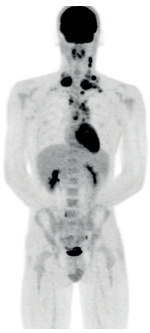
Haematology Nurses & Healthcare Professionals Group



Haematology Nurses and Healthcare Professionals (HNHCP)

Lymphoma in Adults: A Resource for Healthcare Professionals

Dear Colleague

It is with great pleasure that we present the "Haematology Nurses and Healthcare Professionals (HNHCP) – Lymphoma in Adults: A Resource for Healthcare Professionals".

A faculty of specialist nurses working in the field of haematology/oncology, haematologists, and patient advocates have collaborated to develop this programme dedicated to learning about lymphoma.

This programme features topics relevant to the multidisciplinary team approach to caring for patients with lymphoma and their relatives. Nurses, other allied health care professionals and patient organisations play an important role in this process and the group is excited to share with you the most current information and up-to-date recommendations for addressing the unique long-term management of patients' needs.

The Lymphomas Learning Program was made possible by an educational grant from Celgene / Bristol Myers Squibb Company, Incyte, Mundipharma Medical Company, Janssen-Cilag AG, Roche Pharma AG Switzerland and Takeda Pharma AG.

On behalf of the Haematology Nurses and Healthcare Professionals Group and the faculty who worked on this initiative, we hope that the Lymphoma Learning Program will be of value to you in your care of patients with lymphoma.

Sincerely,

Erik Aerts

President

Haematology Nurses and Healthcare Professionals Group

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Lymphoma in Adults: A Resource for Healthcare Professionals is also available online at

www.hemcare.org

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Quick Facts

Lymphomas are characterized by an uncontrolled production and growth of lymphocytes (B or T cells), which often travel to the lymph nodes, spleen, bone marrow, blood and other organs

The main functions of the lymphatic system are:

- Production of immune cells (such as lymphocytes, monocytes and antibody producing cells called plasma cells)
- Removal of interstitial fluid from tissues
- Absorption and transportation of fatty acids and fats as chyle from the digestive system

In active immune response regulation, the lymphatics regulate immune cell entry and migration through the lymphatic system. In passive immune response regulation, the lymphatic system modulates the rate at which antigens and cells are delivered to regional lymph nodes by regulating lymph flow

A biopsy of an affected lymph node or a sample of the tumor is the preferred way to make a definitive diagnosis of lymphoma

Positron emission tomography (PET) combined with computerized tomography (CT) is the preferred method to stage and assess response in lymphomas

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Definition of Lymphomas

Lymphoma is the most common hematologic malignancy. The two main categories of lymphoma are non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) also referred to as Hodgkin disease. Lymphomas are characterized by an uncontrolled production and growth of lymphocytes (B or T cells). These cancerous lymphocytes often travel to the lymph nodes, spleen, bone marrow, blood and other organs.

Because lymphatic tissue is present in many parts of the body, lymphoma can start almost anywhere. It may develop in a single lymph node, a group of lymph nodes, or in other parts of the lymphatic system such as the spleen, bone marrow or other extranodal sites.

Overview of the Lymphatic System

Function

Plasma, along with some white blood cells, routinely moves out of capillaries into the interstitial space. Most of the fluid, approximately 17 of a total of 20 liters, and its constituents is taken up by tissue cells or reabsorbed into the vascular system, depending on the balance of hydrostatic and oncotic pressures. Some of the fluid, certain cells and cellular debris, such as debris from the immune response to local infection, cancer or inflammation, enters the lymphatic system. This fluid is lymph.

Similar to the vascular system, the lymphatic system consists of many thin-walled vessels that transport fluid throughout the body. Smaller lymphatic vessels empty into larger vessels that ultimately drain into the central venous system via the thoracic duct or the right lymphatic duct. Valves facilitate the flow of lymph in one direction, toward the heart. Unlike the vascular system where the pumping action of the heart moves blood through the body, lymph is moved by pressure generated during muscle contraction.

Before entering the central venous system, lymph passes through lymph nodes, which filter out cellular material and foreign particles. During this filtering process, lymphocytes contained within lymph nodes respond to antigens. This immune response involves cellular proliferation, which can cause the nodes to become enlarged. Pathogenic microorganisms carried in the lymphatic fluid can directly infect the nodes causing lymphadenitis. Cancer cells may be present and proliferate in nodes. In addition to removing interstitial fluid from tissues, the lymphatic system also:

- Absorbs and transports fatty acids and fats as chyle from the digestive system
- Produces immune cells (such as lymphocytes, monocytes and antibody producing cells called plasma cells)

Lymphatic function is highly variable and modulated by numerous factors including chronic inflammation, tumors and external stimuli such as radiation, age, obesity and metabolic dysfunction (Kataru 2019).

Components of the Lymphatic System

The components of the lymphatic system are lymph, lymph nodes, lymphatic vessels, collecting ducts, spleen, thymus, tonsils and adenoids, bone marrow, Peyer's patches and the appendix.

Lymph

Also called lymphatic fluid, lymph is a collection of the extra fluid that drains from cells and tissues plus other substances, which include proteins, minerals, fats, nutrients, damaged cells, cancer cells and foreign invaders (e.g., bacteria, viruses). Lymph also transports cells to fight infection, lymphocytes.

Lymph nodes

Lymph nodes are bean-shaped and categorized as being either superficial or deep. Superficial nodes are just below the skin and are present throughout the body. There are collections of lymph nodes in the neck axillae and groin. Smaller nodes (< 1 cm) may be palpable in those areas in healthy people. Deep lymph nodes are those located in the abdominal or thoracic cavity.

There are several hundred lymph nodes in the body, mostly throughout the thorax and abdomen with the highest concentrations in the axillary and inguinal regions (**Figure 1**). Lymph nodes monitor and cleanse the lymph as it filters through them. Nodes also filter out damaged cells and cancer cells and produce and store lymphocytes and other immune system cells that fight and destroy bacteria and other harmful substances. Hence, lymph nodes play a key role in the immune system.

Lymphatic vessels

These vessels are the network of capillaries and a large network of tubes located throughout the body that transport lymph away from tissues toward the heart. Operating very much like veins, lymphatic vessels collect and filter lymph as it moves toward larger vessels called collecting ducts.

Collecting ducts

Lymphatic vessels empty lymph into the right and left lymphatic ducts. These ducts connect to the subclavian vein, which returns lymph to the bloodstream thus assisting the body to maintain normal blood volume and pressure. This also prevents the occurrence of peripheral edema.

Lymphatic nodules

Tonsils and adenoids contain many B and T cells to provide a first line of defense against foreign invaders by trapping pathogens in food and air after entering the body.

Peyer's patches are small masses of lymphatic tissue in the mucous membranes that line the small intestine. The B and T cells located in Peyer's patches monitor the contents of the intestinal lumen for pathogens. Once the pathogen is detected, the B and T cells spread and prepare the body to fight a possible infection.

The spleen is the largest lymphatic organ in the body, located in the upper left quadrant of the abdomen and measuring approximately 10 cm in diameter. It is comprised of lymphatic tissue (mainly lymphocytes) called white pulp, and venous sinuses filled with blood and lymphatic cells (lymphocyte and macrophages) called red pulp. White pulp is found within the red pulp surrounding the arterioles of the spleen. It is made of lymphatic tissue and contains many B and T cells, and macrophages to fight infections. Red pulp, which makes up most of the spleen's mass, contains reticular tissues whose fibers filter worn out

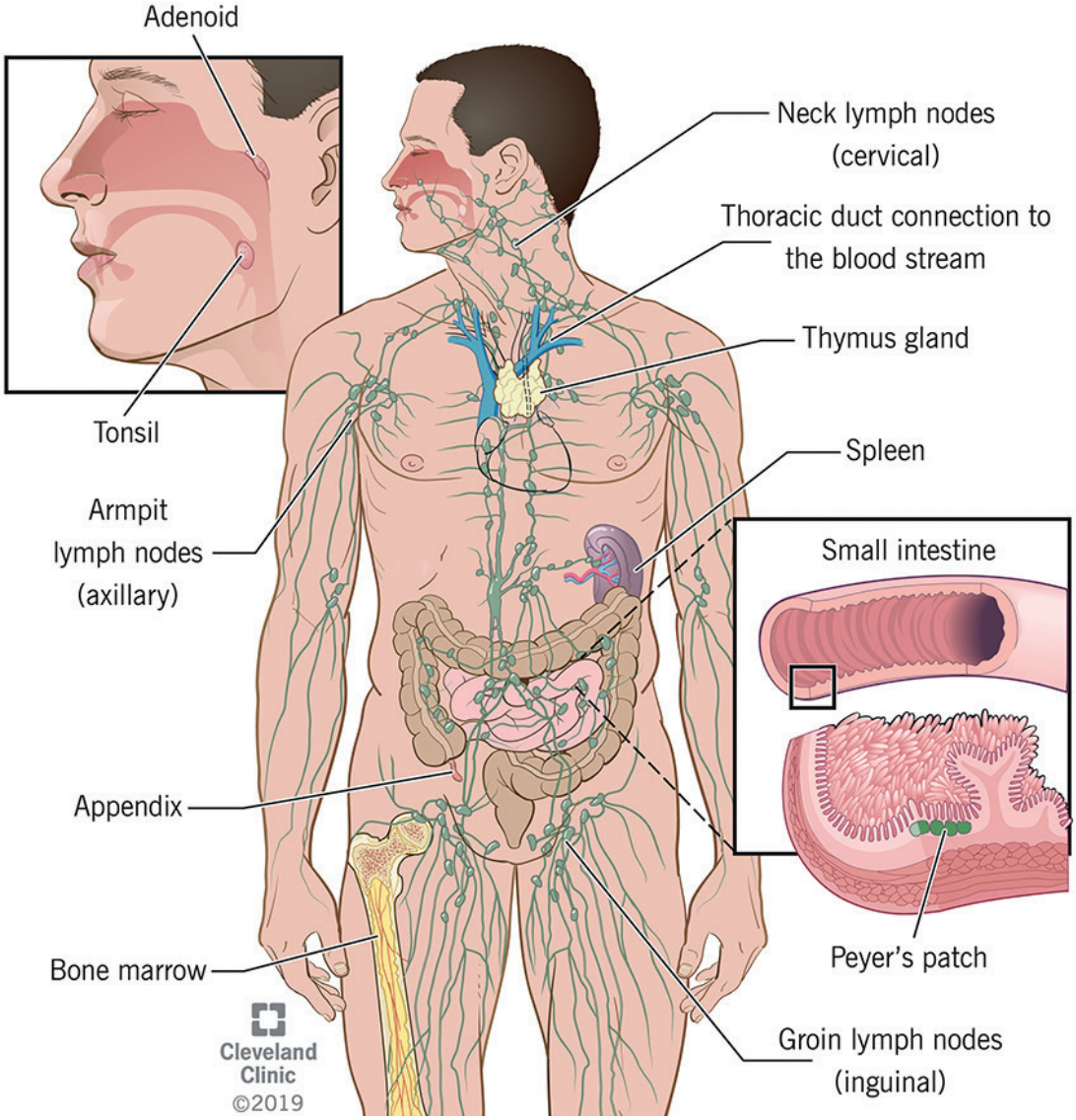

Figure 1. The lymphatic system. The lymphatic system is a network of lymphatic vessels and ducts that transports the lymph back into the circulatory system for recirculation through the body. The lymphatic system is part of the immune system. Source: Cleveland Clinic 2019.

or damaged red blood cells from the blood. Macrophages in the red pulp digest and recycle the hemoglobin of the captured red blood cells. The red pulp also stores many platelets to be released in response to blood loss. The spleen filters and stores blood and produces white blood cells and is a critical part of the immune system.

The thymus is a soft organ located posterior to the sternum. While the thymus is relatively large in infants and small children, its size reduces after puberty and it is relatively small in adults. T cells are produced and mature in the thymus and are released in response to infection. By the time a person reaches puberty, the immune system is mature and the role of the thymus is diminished. After puberty, the inactive thymus is slowly replaced by adipose tissue.

Bone marrow

The soft, spongy tissue in certain bones, such as the hip- and breastbones that produces white and red blood cells and platelets.

Appendix

The appendix contains lymphoid tissue that destroys bacteria before it breaks through the intestinal wall during absorption. The appendix may play a role in storing good bacteria and repopulating the gut with this good bacteria after an infection has subsided.

Disorders of the Lymphatic System

Any failure of the lymphatic vasculature to take up fluid, leaking out of blood capillaries into interstitial spaces in the tissue, and to return this fluid (lymph) to the blood circulation can cause lymphedema (Cueni 2008). In solid tumors, cancer cells exploit the lymphatic vascular system as a route for metastasis.

Disorders of the lymphatic system involve one or more of the following:

Disorder	Outcome
Obstruction	Can lead to accumulation of lymphatic fluid in tissues (lymphedema) and often occurs as a result of surgery, radiation therapy or injury
Infection	Can cause reactive lymph node enlargement (lymphadenopathy) or the nodes themselves may become infected (lymphadenitis) by organisms spreading through the lymphatic system from the primary site of infection. Palpable enlargement occurs when nodes are generally > 1 cm and ≥ 1 lymph node is affected. Lymphadenopathy may be localized (present in 1 body area) or generalized (present in ≥ 2 body areas). Lymphadenitis is lymphadenopathy with pain and/or signs of inflammation (eg, redness, tenderness).
Cancer	Some types of cancer may metastasize to local or regional lymph nodes. A rare form of cancer, lymphangiosarcoma, develops in the lymphatic system

The Role of the Lymphatic System in Immunity

Immunity is the capability of multicellular organisms to repel and resist harmful microorganisms. The nonspecific responses are the first line of defense while highly specific responses are the second line of defense and are tailored to an individual threat.

The traditional belief regarding the role of the lymphatic system in immunity was that it played a passive role in the regulation of immune responses by transporting bacteria, foreign antigens, particulate matter, exosomes and immune cells to regional lymph nodes and lymphoid structures (Kataru 2019). The regulation of immune responses occurs at multiple levels and is both active and passive in nature. Active regulation of immune response by the lymphatics includes regulation of immune cell entry and migration through the lymphatic system. Inactive immune response regulation occurs when the lymphatic system modulates the rate at which antigens and cells are delivered to regional lymph nodes through regulation of vessel tone and pumping (Randolph 2017). Recent evidence suggests that lymphatic endothelial cells regulate immune responses more directly by modulating entry of immune cells into lymphatic capillaries, presenting antigens on major histocompatibility complex proteins and modulating antigen presenting cells (Kataru 2019).

Lymphoid stem cells are derived from multipotent hematopoietic stem cells in the bone marrow. Lymphoid stem cells produce T-lymphocytes and B-lymphocytes (**Figure 2, Table 1**).

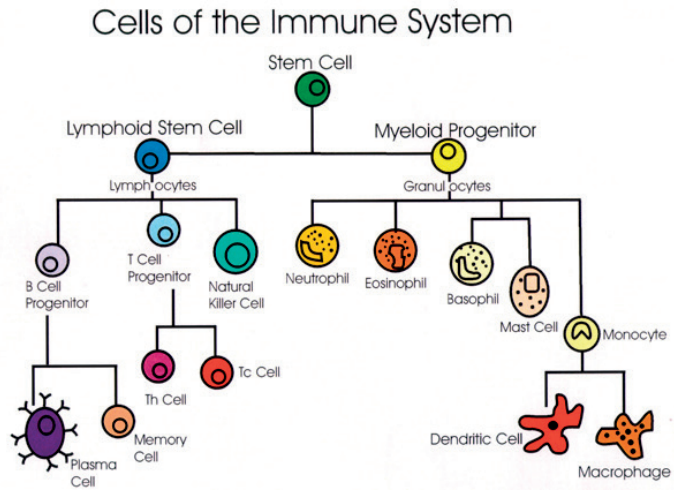

Figure 2. Cells of the immune system. All cells are derived from a multipotent stem cell in the bone marrow. Lymphoid stem cells produce B- and T-lymphocytes and Natural Killer (NK) cells.

Table 1: Characteristics of B- and T-lymphocytes and Natural Killer Cells		
Type of cell	**Origin**	**Function**
B cells	Mature in bone marrow; involved in humoral immune response, essential component of adaptive immune system	Become plasma cells; plasma cells produce and secrete antibodies after antigen exposure, present antigens to T cells
T cells	Mature in thymus; involved in cell-mediated immunity, component of adaptive immune system	Subdivided into helper and cytotoxic T cells; helper T cells release cytokines to stimulate defense against specific antigen; cytotoxic T cells have TCR receptors on surfaces which kill viral cells when receptor matches viral antigen
Natural Killer (NK) cells	Develop in bone marrow; component of adaptive immune system	Provide rapid response to virally infected cells and respond to tumor cells in adaptive immune response; cause cell death through apoptosis. Can recognize stressed cells in the absence of antibodies and MHC while maintaining tolerance to normal, healthy cells
MHC, major histocompatibility complex Based on content from Noonan 2015; Warrington 2012		

Overview of Types of Lymphoma

Lymphoma starts with a change to a single lymphocyte. The changed lymphocytes are categorized as malignant because they proliferate and live longer than normal lymphocytes. The lymphoma cells form masses, which can be present in the lymph nodes or in other parts of the body. Lymphomas represent the most common hematologic malignancy.

The World Health Organization (WHO) lymphoma classification comprises more than 80 entities of mature lymphoid neoplasms (B-cell, T-cell and Hodgkin lymphomas), which range from indolent or slow growing types to those that are highly aggressive (de Leval 2020) (**Table 2**). Lymphomas can affect any component of the lymphatic system. Typically, lymphomas are divided into two categories: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL).

Table 2: Overview of Selected Types of Lymphoma	
Type	**Description**
Hodgkin lymphoma (HL)	Often initiates in the lymph nodes, can spread via contiguous spread from one lymph node to another or to other organs; less common than NHL. There are two major classifications of HL: classic and nodular lymphocyte predominant
Classical HL (cHL)*	Accounts for about 93% of HL cases; subtypes include nodular sclerosis cHL, mixed cellularity cHL, lymphocyte-rich cHL and lymphocyte-depleted cHL
Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)	A rare mature B-cell lymphoma representing about 5% of HL cases. Usually affects young adult males. Primarily involves lymph nodes and is more localized at diagnosis. May progress to diffuse large B-cell lymphoma.
Non-Hodgkin Lymphoma (NHL)	A group of several closely related cancers called lymphoid neoplasms with over 50 different subtypes. There are two broad categories of NHL: B-cell lymphomas and T-cell lymphomas
Diffuse large B-cell lymphoma (DLBCL)*	Most common type of non-Hodgkin lymphoma (NHL). Affects B-lymphocytes, aggressive type; several subtypes which differ with respect to certain characteristics.
Follicular lymphoma	Approximately one in 5 lymphomas diagnosed in the U.S. are follicular lymphoma. Commonly starts in lymphocytes and there is a higher frequency in older adults. Usually slow growing; first-line treatment is often watchful waiting
Cutaneous B-cell lymphoma	Extranodal lymphoma that originates in the skin without evidence of disease outside of the skin. Account for ~ 20% to 25% of all primary cutaneous lymphomas. Primary cutaneous B-cell lymphomas occur when the lymphoma cells originate in B-lymphocytes. Often indolent. Can recur in new places on the skin but rarely in other body systems. Highly characteristic clinical and histologic features, clinical behavior, prognosis and treatment different from that of nodal forms of lymphoma.
T-cell lymphoma	Can develop in lymphoid tissues such as the lymph nodes and spleen, or outside of lymphoid tissues (i.e., gastrointestinal tract, liver, nasal cavity, skin)

Table 2: Overview of Selected Types of Lymphoma	
Type	**Description**
Cutaneous T-cell lymphoma	One of the most common forms of T-cell lymphoma; account for ~ 75% - 80% of all primary cutaneous lymphomas. Most commonly involves the skin but can involve the blood, lymph nodes and other organs. Highly characteristic clinical and histologic features, clinical behavior, prognosis and treatment different from that of nodal forms of lymphoma
Peripheral T-cell lymphoma*	A rare and fast-growing group of lymphoma that arises from mature T lymphocytes
Burkitt's lymphoma	A rare type of NHL that is aggressive and most common in people with compromised immune systems
Chronic lymphocytic leukemia	An indolent B-cell NHL, accounts for ~ 18% of cases of NHL. Primarily occurs in blood and bone marrow, occasional involvement of lymph nodes or spleen. WBC is elevated at presentation in the absence of symptoms
Mantle cell lymphoma	An aggressive form, rare occurrence, rare cases of indolent presentation. More commonly diagnosed at a later stage and it usually occurs in or involves the gastrointestinal tract or bone marrow
*Addressed in depth in this learning program Swerdlow 2016; Willemze 2019	

Non-Hodgkin lymphoma (NHL) is the seventh most common cancer in both men and women and accounts for 4% of all cancers in the U.S. In Europe in 2012, lymphomas accounted for nearly 2.5% of all deaths from cancer (Lymphoma Coalition 2020) (**Table 3**). NHL is far more common in adults and risk increases with age. Of interest, the number of persons diagnosed with Hodgkin lymphoma (HL) has steadily declined. See Module 2 and Module 3 for more specific information on HL and NHL statistics, respectively.

Table 3. Estimated Numbers of New Cases and Deaths from Lymphoma (thousands) in Europe in 2018						
	Incidence			**Mortality**		
	Cases, both sexes (% all cancer)	Cases, male (% all cancer)	Cases, female (% all cancer)	Cases, both sexes (% all cancer)	Cases, male (% all cancer)	Cases, female (% all cancer)
Hodgkin lymphoma	19.2 (0.5%)	10.5 (0.5%)	8.7 (0.5%)	4.3 (0.2%)	2.4 (0.2%)	1.9 (0.2%)
Non-Hodgkin lymphoma	115.1 (2.9%)	62.4 (3.0%)	52.7 (2.8%)	48.1 (2.5%)	26.3 (2.4%)	21.8 (2.6%)
Adapted from: Ferlay 2018						

Initial Evaluation of Lymphoma

Diagnosis

The diagnosis of lymphoma depends on morphology, immunohistochemistry and flow cytometry, which should be reviewed by a pathologist experienced in hematology and/or proliferative diseases. Molecular studies are required to accurately categorize the lymphoma. Prognostic indices, molecular profiling and more accurate imaging have led to improvements in disease characterization and treatment selection (Barrington 2014). [More detailed information on the diagnosis of HL and NHL is available in Module 2 and Module 3, respectively.]

Lymph node assessment

A biopsy of an affected lymph node or a sample of the tumor is preferred to establish a definitive diagnosis of lymphoma. The use of incisional or excisional biopsy is preferable over fine needle aspiration as these procedures provide sufficient tissue for molecular and genetic studies and carry a lower risk of a false negative result.

Samples of involved lymph nodes or lymphoid tissue should be reviewed by a pathologist. Samples are usually collected using a biopsy or fine needle aspiration procedure. Morphologic examination as well as immunohistochemistry and flow cytometry evaluations are most commonly performed on the specimen.

Bone marrow evaluation

Although iliac crest bone marrow biopsy and aspirate has long been considered the gold standard for evaluating bone marrow infiltration by lymphoma, sampling error because of patchy bone marrow involvement can occur. Morphologic and immunophenotyping evaluation of specimens is frequently performed. Cells can be subjected to analysis of cell surface markers by flow cytometry as well as cytogenetic analysis, both of which may provide key diagnostic information.

Laboratory tests

Complete blood count (CBC) with differential: May be used to rule out other hematologic conditions (such as leukemia).

Molecular genetic analysis: Provides tumor profiling by evaluating the DNA in cancer cells for genetic changes; determines whether all of the cells belong to a single clone. Techniques used in molecular analysis include those that detect proteins (immunophenotyping), messenger ribonucleic acid ([mRNA] in situ hybridization), or changes in deoxyribonucleic acid ([DNA]; Southern blot, polymerase chain reaction [PCR], fluorescent in situ hybridization [FISH] and gene sequencing). Methods are useful for diagnosing subtypes and prognostic assessment and may be of particular relevance if peripheral involvement is suspected.

Immunophenotyping: Can identify the cells involved by testing for the presence or absence of certain markers on the membrane of the cells or inside cells. These commonly used markers are called clusters of differentiation (CD) and are listed numerically. By developing a list of the CDs present on the cells, it is possible to classify the cells. This test can be done by several different methods, including flow cytometry and immunohistochemistry.

Genotyping is performed to detect cytogenetic abnormalities, chromosomal translocations and immunoglobulin or T cell receptor gene rearrangements using FISH, Southern blot hybridization analysis and PCR.

Comprehensive metabolic panel including:

- Serum creatinine: elevated levels may indicate renal disease (nephrotic syndrome), which is associated with Hodgkin lymphoma
- Beta-2 microglubulin (in some patients)
- Lactate dehydrogenase (LDH) to help determine prognosis
- Uric acid
- Evaluation of liver and renal function
- Hepatitis B: often performed on patients who will undergo rituximab therapy because of adverse effects associated with that treatment and hepatitis B
- Heptatitis C and HIV testing (in some patients)

If CNS involvement is suspected, an analysis of cerebrospinal fluid may be performed.

Radiographic imaging

Advancements in imaging are influencing trial design and affecting clinical practice. In fact, the increasing use of CT has made stage laparotomy obsolete. PET combined with CT has replaced PET alone as the preferred method to stage and assess response in lymphomas (Cheson 2014).

Fluorodeoxyglucose (FDG) is a tracer used with PET. Metabolically active malignant lesions, such as those in some forms of lymphoma, take up FDG and are called FDG-avid. The intensity of FDG uptake is higher in aggressive than in indolent lymphomas and FDG is therefore not recommended for use in lymphomas with low FDG avidity. The maximum standardized uptake value (SUVmax), a measure of tissue radioactivity concentration relative to the injected dose of radioactivity per kilogram of body weight, is generally higher in aggressive lymphomas as compared with indolent NHLs, although there are exceptions and disease aggressiveness should not be based on SUVmax alone (El-Galaly 2018).

PET-CT may be used to select best site to biopsy. Baseline PET-CT scans should be available for accuracy in the subsequent assessment of treatment response.

The Deauville five-point scale (**Table 4**) is an internationally recommended scale for routine clinical reporting and clinical trials using PET-CT with FDG for both initial staging and assessment of treatment response in HL and some types of NHL, including diffuse large B-cell lymphoma. The scale (also known as the Deauville criteria) scores the most intense uptake of FDG in a site of initial disease, if present. FDG uptake is graded in relation to the reference regions of normal mediastinum and liver. Each FDG-avid (or previously FDG-avid) lesion is rated independently.

Table 4. Deauville 5-Point Scale

Score	Evaluation criteria
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

A score of 1 or 2 is considered to represent complete metabolic response at interim and end-of-treatment. FDG uptake declines during therapy in chemotherapy-sensitive disease, and residual FDG uptake higher than normal liver uptake is frequently seen at interim in patients who achieve complete metabolic response at the end of treatment. Recent data suggest that most patients with uptake higher than mediastinum but less than or equivalent to liver (score of 3) have good prognosis at the end of treatment with standard therapy in HL and DLBCL. A score of 4 or 5 at interim suggests chemotherapy-sensitive disease, if uptake is reduced from baseline, and is considered to represent partial metabolic response. At end of treatment, residual metabolic disease with a score of 4 or 5 represents treatment failure even if uptake has reduced from baseline. A score of 4 or 5 with intensity that does not change or even increases from both baseline and/or new foci represents treatment failure at interim and end-of-treatment assessments.
Source: Barrington 2014; Cheson 2014

Timing of pretreatment baseline scans should be based on the clinical situation. Whenever possible, the same imaging modality should be used at baseline and subsequent visits.

PET-CT using FDG is preferred over CT alone for staging most lymphomas due to its increased sensitivity. PET-CT is critical as a baseline measurement before therapy to increase the accuracy of subsequent response assessment (**Table 5**).

Table 5. Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies Non-avid disease	PET-CT CT	Increased FDG uptake Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies Non-avid disease	PET-CT CT	Diffuse uptake, solitary mass, miliary lesions, nodules > 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies Non-avid disease	PET-CT CT	Diffuse uptake, mass Nodules
CNS	Signs, symptoms		CT MRI CSF assessment	Mass lesion(s) Leptomeningeal infiltration, mass lesions Cytology, flow cytometry
Other (e.g., skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT*, biopsy	Lymphoma involvement

CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
*PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary
Adapted from Cheson et al 2014

Chest x-ray is no longer required in lymphoma staging because it is less accurate than CT. A CT scan provides better differentiation of a single large nodal mass versus an aggregate of individual nodes. Contrast-enhanced CT provides a more accurate measurement of nodal size, often a requirement for entry onto a clinical trial, more accurately distinguishes bowel from lymphadenopathy, and identifies compression/thrombosis of central/mediastinal vessels. Nowadays, most PET scanners are integrated PET-CT scanners.

Magnetic resonance imaging (MRI) helps characterize skeletal and intracranial lesions, which may be difficult to assess with PET-CT. MRI is the modality of choice for suspected CNS lymphoma (Barrington 2014).

Patient Evaluation

Clinical evaluation should include individual patient characteristics (i.e., age, sex) and a comprehensive history including assessment for the presence of fevers of more than 38o C, chills, drenching night sweats or unexplained weight loss of more than 10% of body mass over 6 months and a history of malignancy. While the presence of symptoms may not necessarily influence treatment, they do factor into prognosis and their recurrence may be indicative of disease recurrence [see Module 2, Diagnosis of Hodgkin Disease]. Unexplained enlargement of lymph nodes as well as enlargement of the liver and spleen are positive findings. Palpation and measurement of organs and lymph nodes may vary and it is therefore helpful to perform CT imaging to obtain more accurate measurements.

Techniques used in Staging Lymphoma

Staging defines disease location and extent, provides information for estimating prognosis, allows comparison of data between studies and provides a baseline from which treatment response or disease progression can be compared (Cheson 2014). Staging is now one component of factors in prognostic indices increasingly used for pretreatment risk stratification and treatment selection.

Staging schema

PET-CT improves the accuracy of staging, which ensures that fewer patients are over- or under-treated and provides a baseline for subsequent response assessment. Performing these scans is particularly important for staging prior to initiation of radiation therapy.

During the staging process, the location of the lymphoma is evaluated (on one or both sides of the diaphragm), and whether the lymphoma affects nodes and organs of the lymphatic system (lymphatic sites) or areas outside of the lymphatic system (extranodal or extralymphatic sites). Extranodal sites include the lungs, liver, blood, bone marrow, kidneys, brain and spinal cord (**Table 6, Figure 3**).

For HL and the most common aggressive NHLs (e.g., DLBCL and peripheral T-cell lymphomas), disease staging is not a matter of disease curability but rather of cure likelihood and the consistent upstaging by PET-CT will likely lead to a shift toward more intensive first-line therapies (El-Galaly 2018).

Table 6. Revised Staging System for Primary Nodal Lymphomas (Lugano modification of the Ann Arbor staging system[a])

Stage	Nodal Disease	Extranodal Disease
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on either side of diaphragm	Stage I or II with limited contiguous extranodal involvement
II bulky[b]	II as above with bulky disease	Not applicable
Advanced		
III	Nodes on both sides of diaphragm; nodes above diaphragm with spleen involvement	Not applicable; nodal stage II plus extranodal involvement constitutes stage IV disease
IV	Additional noncontiguous extra-lymphatic involvement	Not applicable

[a] Extent of disease is determined by PET-CT for avid lymphomas
[b] Treatment of II bulky disease as limited or advanced may be determined by histology and a number of prognostic factors
Source: Cheson 2014; Cheson 2016

Patients are generally treated based on limited (stages I and II, nonbulky) or advanced (stages III or IV) disease, with stage II bulky disease considered limited or advanced as determined by histology and a number of prognostic factors [see Modules 2 and 3 for more detailed information on staging of HL and NHL, respectively].

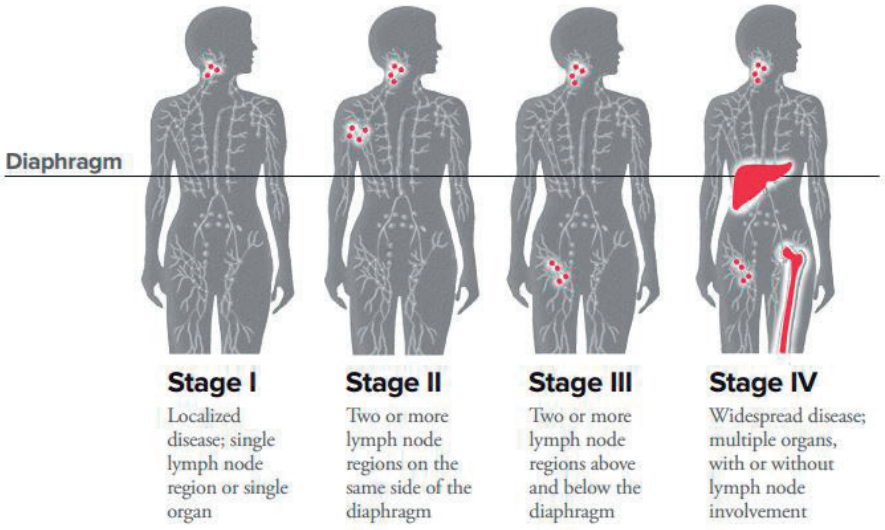

Figure 3. Staging schema for lymphomas. The stage identifies the location of the disease, it does not reflect how well or how poorly a patient may respond to treatment. Source: Leukemia & Lymphoma Society 2020

Recommended role of PET-CT for staging:

- PET-CT should be used for staging but is not routinely recommended in lymphomas with low FDG avidity; PET-CT may be used to select the best site for obtaining a node biopsy
- Contrast-enhanced CT when used at staging or restaging should ideally occur during a single visit and combined with PET-CT; baseline findings will determine whether contrast-enhanced PET-CT or lower-dose unenhanced PET-CT will suffice for additional imaging examinations
- Bulk remains an important factor in some lymphomas; volumetric measurement of tumor bulk and total tumor burden, including methods combining metabolic activity and anatomical size or volume, should be explored as potential prognostic indicators (Barrington 2014)

Evaluation of tumor bulk

Bulk is generally assessed using PET-CT imaging. Bulk is a negative prognostic factor and there is little agreement on its definition, which is disease, stage and treatment specific. In diffuse large B cell lymphoma and HL, for example, bulky disease is generally defined as any nodal or extranodal tumor mass with a diameter of ≥ 7.5 cm.

Evaluation of organ involvement

PET-CT is recommended to diagnose spleen involvement, which may be characterized by homogeneous splenomegaly, diffuse infiltration with miliary lesions, focal nodular lesions or a large solitary mass. The spleen may be of normal size and still contain lymphoma. Enlargement of the spleen may be due to non-lymphoma-related causes such as an increase in blood volume or the use of hematopoietic growth factors. The Lugano classification uses a cutoff for splenomegaly of more than 13 cm in vertical length.

Assessment of liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by lymphoma. Therefore, PET-CT scans are recommended to identify liver involvement.

Evaluation of bone marrow involvement

Although bone marrow biopsy has been a standard in lymphoma staging, the high sensitivity of PET-CT for bone marrow involvement is preferred. Bone marrow involvement is rare in early-stage disease in the absence of a suggestive PET finding, and involvement is rare in advanced stage disease in the absence of disease-related symptoms or other evidence of advanced-stage disease. If a PET-CT is performed, bone marrow aspirate/biopsy may not be required for routine bone marrow evaluation.

Risk Stratification

The International Prognostic Index (IPI) was developed as a model for predicting outcomes, including risk of relapse, in patients with lymphoma on the basis of the patients' clinical characteristics before treatment. IPI is one of several scoring systems used to assess risk in lymphoma [see specific information in Modules 2 and 3].

Response Criteria used in Lymphoma

PET-CT is generally superior to CT assessment alone for monitoring therapy and is recommended for assessment of both early treatment response and, at the end of treatment, to establish remission status. At the end of treatment, PET can be predictive of disease remission in some types of lymphoma (Barrington 2017).

FDG may be taken up in inflammation induced by treatment. Therefore, to minimize inflammatory uptake, imaging should be delayed for a minimum of 3 weeks (preferably for 6 to 8 weeks) after chemotherapy at the end of treatment, 2 weeks after granulocyte colony-stimulating factor (GCSF) treatment and 3 months after radiotherapy (Barrington 2017).

One of the most important factors that determine response to therapy is related to the effect of treatment on the aggregate dimensions of all target lesions. The Lugano lymphoma response criteria (**Table 7**) are commonly used and estimate the tumor burden by using the sum of the products of the longest perpendicular diameters, which is calculated by multiplying the two longest perpendicular diameters for each target lesions. By contrast, the newer RECIST 1.1 criteria (**Table 8**) estimate tumor burden using the sum of diameters of target lesions (longest diameter for non-nodal lesions and short axis for nodal lesions).

Many novel targeted agents may alter glucose uptake and/or metabolism and therefore normalizing of FDG-PET imaging alone is not sufficient by itself to determine complete response (CR) status unless accompanied with a significant (>30%) decrease in the sum of diameters. Additionally, immunomodulating agents, such as lenalidomide, and new immunotherapies such as immune check point inhibitors, in addition to cell therapy with chimeric antigen receptor engineered T cells (CAR-T) can be associated with a "pseudo-progression" that may be related to recruitment of immune cells to the disease site (Younes 2017). This means, following activation of T cells, the tumor lesion may transiently increase in size before shrinking: therapies should not be prematurely terminated but rather further scans performed to evaluate treatment response.

Fertility and Pregnancy Counseling

As some types of chemotherapy and abdominal radiotherapy can cause permanent infertility, reproductive counselling and consideration of sperm banking, oocyte collection or ovarian tissue cryopreservation should be offered to patients of reproductive age before treatment (Eichenauer 2018).

Table 7. Criteria for Response Assessment

PET-CT-based response				
	CR	**PR**	**SD or no response**	**PD**
Lymph nodes and extralymphatic sites	PET-CT score 1, 2 or 3[1] with or without a residual mass on 5PS or on CT, target nodes/ nodal masses must regress to ≤1.5cm in LDi	PET-CT score 4 or 5 on 5PS with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease. At end-of-treatment, these findings indicate residual disease	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end-of-treatment	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment
Bone marrow involvement	No evidence of FDG-avid disease in marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline	No change from baseline	New/recurrent FDG-avid foci
New lesions	None	None	None	New FDG-avid foci consistent with lymphoma

[1]A score of 3 in many patients indicates a good prognosis with standard treatment. 5PS, 5-point scale (Deauville); CR, complete response; CT, computerized tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; LDi, longest diameter; PD, progression of disease; PR, partial response; SD, stable disease.
Source: Cheson 2014; Barrington 2017

Table 8. RECIST 2017: Response Categories based on Assessment of Target Lesions

% Change in sum of diameters of target lesions from nadir					
	CR	**PR**	**MR[1]**	**SD**	**PD**
% change from baseline	• Complete disappearance of all target lesions and all nodes with long axis <10 mm • ≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	• >20% increase in the sum of longest diameters of target lesions • For small lymph nodes measuring <15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm • Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauville score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

[1]A provisional category. CR, complete response; CT, computerized tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease
Source: Younes 2017

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Quick Facts

- While no clearly defined risk factors for developing Hodgkin lymphoma have been identified, people testing positive for Epstein-Barr virus (EBV) seem to be at higher risk of developing the disease
- The hallmark characteristic of Hodgkin lymphoma is the presence of Reed-Sternberg cells, which are large abnormal lymphocytes
- The presence of "B" symptoms, which frequently occur in patients with advanced-stage disease, has an impact on prognosis
- Chemo- and radiation therapy are the mainstays of treatment providing excellent survival rates even in patients with advanced-stage disease
- Standard therapy for both limited and advanced disease is adriamycin, bleomycin, vinblastine and dacarbazine (ABVD), a regimen providing an acceptable balance of efficacy and toxicity
- Escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone (escBEACOPP) show survival advantages over ABVD
- The monitoring for secondary complications is of great importance in survivors of Hodgkin lymphoma; the risk of death from cardiovascular disease and second malignancies increases with time
- PET-guided treatment continues to improve outcomes including the reduction of treatment-related side effects

Module II: Hodgkin Lymphoma in Adults: Diagnosis – Staging - Treatment

A. Overview of Hodgkin Lymphoma (HL)

B. Epidemiology and Pathogenesis

C. Classification

D. Clinical Presentation and Initial Work-up

E. Staging and Risk Assessment

F. Treatment

1. Treatment considerations in HL
2. Front-line treatment for limited-, intermediate- and advanced-stage disease
3. Treatment for refractory/relapsed disease

G. Evaluation of Treatment Response

H. Follow-up, Long-term Implications and Survivorship

I. Future Perspective on treating Hodgkin Lymphoma

Overview of Hodgkin Lymphoma (HL) in Adults

Hodgkin lymphoma (HL) (also called Hodgkin's lymphoma, Hodgkin's disease and lymphogranulomatosis) is a clearly defined malignant disease of the lymphatic system. Sir Thomas Hodgkin first identified and described HL in 1832. In HL, the presence of malignant Hodgkin and Reed-Sternberg (HRS) cells is disease defining. These cells were first described in 1898 by Carl Sternberg and subsequently by Dorothy Reed in 1902. Most likely, the origin of HRS cells is the germinal center B cells (Renner 2018).

Epidemiology and Pathogenesis

HL is a relatively rare disease with 3 to 5 new cases/100,000 inhabitants and accounts for approximately 10% of cases of newly diagnosed lymphoma in the U.S. (Shanbhag 2018). According to SEER data, there will be an estimated 8,480 new cases of HL in the U.S. in 2020 representing 0.5% of all new cancer cases (SEER, 2020). The estimated incidence of HL in Europe in 2018 was 2.7% with a mortality rate of 0.5% (all ages) (ECIS 2020). Moreover, globally the estimate of new cases of HL in 2018 was 79,790 (0.4% of all cancers) with an estimated 26,167 deaths (0.3% of all cancer deaths) (Bray 2018).

The majority of patients diagnosed with HL are male and the median age at diagnosis is 39 years with a higher frequency in persons aged 20 to 34 years who comprise almost one-third of newly diagnosed patients (Shanbhag 2018). A second age-related increased incidence is the occurrence of HL in adults aged > 55 years (Ansell 2018).

The etiology of HL is not clearly understood and there are no clearly defined risk factors for the disease. Infectious agents, particularly Epstein-Barr virus (EBV) may be involved in the pathogenesis. Exact numbers differ, but most data show that up to 30% of cases of classic HL (cHL) may be positive for EBV proteins. Similarly, the risk of developing cHL after EBV infection increases. The exact mechanism by which EBV can lead to HL, however, is unknown. Other factors associated with the development of HL include immunosuppression, as occurs with human immunodeficiency virus (HIV), in association with highly active antiretroviral therapy (HAART) or after solid organ transplantation, and a genetic predisposition (i.e., family member with HL).

Classification

There are two distinct disease entities in HL based on morphology and immunohistochemistry: classical HL (cHL) and the rare nodular lymphocyte predominant HL. Over 90% of cases are of cHL, which behaves as an aggressive neoplasm, whereas lymphocyte predominant HL has an indolent biology in most instances (Shanbhag 2018). This chapter will focus on cHL.

In cHL, the neoplastic cell is the Reed-Sternberg cell. These cells comprise only 1% to 2% of the total tumor cell mass. The remainder is composed of a variety of reactive, mixed inflammatory cells consisting of lymphocytes, plasma cells, neutrophils, eosinophils and histocytes. Reed-Sternberg cells are large, abnormal lymphocytes that may contain more than one nucleus (**Fig. 1**).

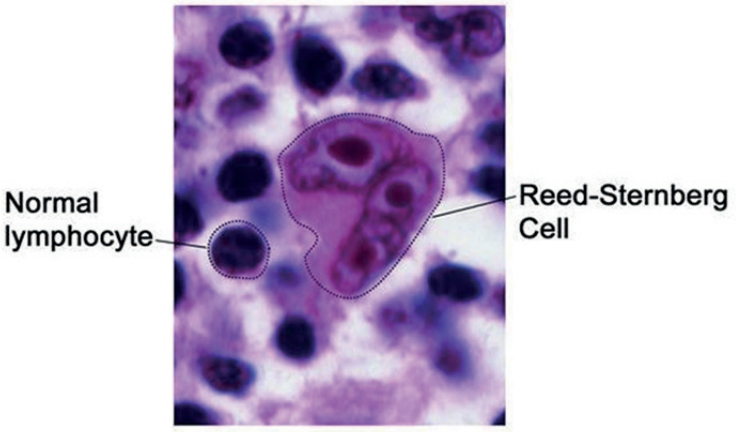

Figure 1. Image of normal lymphocyte and Reed-Sternberg cell. Image courtesy of National Cancer Institute.

The Hodgkin and Reed-Sternberg cells stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45. CD30 is a marker of lymphocyte activation that is expressed by reactive and malignant lymphoid cells and was originally identified as a cell surface antigen on Reed-Sternberg cells. CD15 is a marker of late granulocytes, monocytes, and activated T-cells that is not normally expressed by cells of B lineage.

Classical HL has four histological subtypes, each with its own unique clinical features (**Table 1**).

Table 1. Subtypes of Classical Hodgkin Lymphoma
Nodular sclerosis: most common subtype accounting for over 90% of cases of cHL, tends to affect young adults; usually presents with localized disease involving cervical, supraclavicular and mediastinal regions; better prognosis overall than other subtypes of cHL
Mixed cellularity: comprises 20% to 30% of cHL; more frequent in patients with HIV infection; commonly associated with a more advanced stage of disease and poorer prognosis
Lymphocyte depleted: low incidence (<1% of cases); occurs mainly in older age patients and patients with acquired immune deficiency syndrome; symptomatic extensive disease without peripheral lymphadenopathy common at presentation; aggressive disease course compared with other cHL subtypes, unfavorable prognosis
Lymphocyte rich: comprises about 5% of all cHL; similar to nodular lymphocyte predominant HL although Reed-Sternberg cells have a more classical immunophenotype consistent with cHL; patients tend to have peripheral adenopathy without bulky mediastinal involvement, usually present with early-stage disease; favorable prognosis

Clinical Presentation and Initial Work-up

A variety of benign and malignant lymphoid proliferations can display histological features resembling HL emphasizing the importance of a complete clinical history and an adequate excisional biopsy for proper diagnosis (Wang 2019). To confirm the diagnosis, it is necessary to identify the malignant Reed-Sternberg cell, which is of follicular center B-cell origin, within the appropriate cellular environment of normal reactive lymphocytes, eosinophils and histocytes using lymph node biopsy.

Most patients with cHL present with supradiaphragmatic lymphadenopathy, which is usually painless (**Table 2**). A majority of patients present with cervical, anterior mediastinal, supraclavicular and axillary lymph node involvement, inguinal areas are less frequently involved [see Module 1]. Mediastinal masses can grow quite large before a diagnosis is made. Although contiguous lymph node groups are most frequently involved, HL may also affect extranodal tissues by either direct invasion or hematogenous spread. The most common extranodal sites are the spleen, lungs, liver and bone marrow.

Approximately one third of patients present with "B" symptoms, which are frequent in patients with advanced-stage or bulky disease and are prognostic and therefore included in staging systems.

„B" symptoms:

- Fever, chills
- Drenching night sweats
- Weight loss >10% of body weight
- Fatigue, pruritus and alcohol-induced pain

(Ansell 2018; Eichenauer 2018; Cheson 2014)

Table 2. Diagnostic Workup in Hodgkin Lymphoma			
Medical History and Physical Exam	**Diagnosis**	**Radiologic/imaging tests**	**Pretreatment examinations**
Presence of "B" symptoms, fatigue, pruritus, alcohol-induced pain Measurement of nodal groups, size of liver and spleen below costal margins in midclavicular line	Lymph node biopsy (or biopsy from another organ with suspected involvement)	PET-CT with FDG of whole body CT scan of chest, neck, abdomen Chest x-ray	Full blood cell count; ESR; blood chemistry; HBV, HCV and HIV screening; ECG, Echocardiography, Pulmonary function test; Reproductive counselling; Serum pregnancy test
CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency viruses; PET, positron emission tomography Adapted from: Eichenauer 2018			

Mediastinal bulk, an unfavorable prognostic factor in patients with early-stage HL, is measured most commonly using the mediastinal mass ratio (MMR). The MMR is the ratio of the maximum width of the mass and the maximum intrathoracic diameter: any mass with MMR > 0.33 is defined as bulky disease. Another definition of bulk is any single node or nodal mass that is ≥ 10 cm in diameter (Cheson 2014). Other definitions are also used in practice.

Staging and Risk Assessment

The Ann Arbor staging system may be used for anatomic distribution of disease extent, but includes antiquated procedures such as liver biopsy, laparotomy and bone marrow trephine for initial staging. The Lugano staging and response assessment, which is based on the Ann Arbor staging system, is fairly new and not yet universally accepted. Disease stage is only one component of factors in prognostic indices increasingly used for pretreatment risk stratification and selection of therapy (Shanbhag 2018). The staging system for patients with HL is based on:

- whether the involved lymph nodes are on one or both sides of the diaphragm,
- the number of involved sites,
- whether the sites of involvement are bulky,
- whether there is contiguous extranodal involvement or disseminated extranodal disease and
- the presence of typical systemic symptoms (B symptoms) (Ansell 2018).

As applies to most lymphomas, whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) has very high sensitivity and specificity and is the preferred method of staging cHL (see Module 1). PET-CT can detect extranodal disease with higher sensitivity than CT alone, both in the bone marrow and other organs (El-Galaly 2018). This method also has a consistent influence on staging, with upstaging of approximately 15% to 25% of patients and downstaging in only a small minority of patients. The tendency toward upward staging is important because HL is a disease where early and advanced stages are treated very differently. The 5-point Deauville scale is used to interpret PET findings for staging purposes (see Module 1).

Treatment is based on classifying patients as having limited/early stage disease, intermediate or advanced (stage III or IV) disease (**Table 3**).

Table 3. Definition of Limited, Intermediate and Advanced Stages of Hodgkin Lymphoma according to the EORTC/LYSA and the GHSG

	Stage according to EORTC/LYSA	Stage according to GHSG
Treatment group		
Limited/early stage	I to II without risk factors (supradiaphragmatic)	I to II without risk factors
Intermediate stage	I to II with ≥ 1 risk factors (supradiaphragmatic)	I, II"A" with ≥ 1 risk factors IIB with risk factors C and/or D, but not A/B
Advanced stage	III to IV	II"B" with risk factors A and/or B III to IV
Risk factors[1]	A: large mediastinal mass[2] B: age ≥ 50 years C: elevated ESR[3] D: ≥ 4 nodal areas[4]	A: large mediastinal mass[2] B: extranodal disease C: elevated ESR[3] D: ≥ 3 nodal areas[4]

[1] Risk factors are defined differently by various professional organizations and study groups
[2] Large mediastinal mass: mediastinum-to-thorax ration ≥ 0.35 (EORTC/LYSA); mediastinal mass larger than one-third of the maximum thoracic width (GHSG).
[3] Elevated ESR: > 50 mm/h without B symptoms, > 30 mm/h with B symptoms (B symptoms: fever, night sweat, unexplained weight loss >10% over 6 months)
[4] Nodal areas: involvement of ≥ 4 out of 5 supradiaphragmatic nodal areas (EORTC/LYSA); involvement of ≥ 3 out of 11 nodal areas on both sides of the diaphragm (GHSG)
Suffix "A", no detectable B symptoms; suffix "B", presence of B symptoms
EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; LYSA, Lymphoma Study Association
Source: Eichenauer 2018

Patient prognosis is largely based on the stage of the disease and various prognostic factors, which may be defined differently across various major cooperative groups (e.g., German Hodgkin's Study Group, European Organization for Research and Treatment of Cancer [EORTC]).

In patients with advanced HL, disease bulk and other traditional prognostic variables have been found to be less predictive of outcome. For these patients, the International Prognostic Score (IPS) was developed and assessed in clinical trials (Hasenclever 1998) (**Table 4**). According to trial results, patients with five or more factors were found to have a 5-year freedom from progression of 42% while patients with no negative prognostic factors had an 84% likelihood of being free from progression at 5 years (Hasenclever 1998).

Table 4. International Prognostic Score (IPS) for Advanced HL

Risk factors	Categorization based on number of risk factors[1]
Age ≥ 45 years Stage IV disease Male sex Leukocytosis: WBC > 15,000 g/L Lymphopenia: lymphocyte count < 0.6 g/L or < 8% of WBC Serum albumin < 4 g/L Hemoglobin < 10.5 g/L	Good risk: IPS 0-1 Fair risk: IPS 2-3 Poor risk: IPS 4-7

[1] One point is given for each present risk factor
Source: Hasenclever 1998

Treatment

Treatment considerations in HL

HL is a success story in cancer with a 1-year survival rate of approximately 92% and an estimated 5-year survival rate of 86%. Even in patients with advanced-stage HL, outcomes with contemporary treatment approaches are very good. Chemotherapy and radiation therapy are the mainstays of cHL treatment. Standard therapy for both limited and advanced disease is adriamycin, bleomycin, vinblastine and dacarbazine (ABVD), a regimen providing an excellent balance of efficacy and toxicity (**Table 5**). Inferior outcomes, however, are still prevalent in two subgroups of patients following standard therapy; namely, those older than 60 years and the adolescent and young adult population (Spinner 2018). The 5-year survival for adult patients diagnosed with cHL is 87.4% (2010-2016 data, SEER 2020).

The use of modern treatment strategies means that 80% to 90% of patients with HL achieve permanent remission and can be considered cured. Although the risk of relapse in cHL decreases after 2 years, up to 30% of patients with advanced-stage and 5% to 10% with limited-stage cHL experience relapse (Hapgood 2016).

Debate exists as to whether or not radiotherapy is required in all patients, especially those with early stage HL due to late toxic effects of radiotherapy. The PET-guided response-adapted approach to treatment, which often leads to treatment de-escalation, may be beneficial in moving toward the goal of maximizing cure while minimizing treatment toxicities.

The predominant factors that determine the initial choice of therapy are:

- anatomical stage of disease (limited or advanced)
- presence of poor prognostic features
- presence of constitutional symptoms
- presence of bulky disease (Ansell 2018).

Generally, initial treatment combines abbreviated courses of combination chemotherapy followed by involved-field radiation for patients with early stage disease and longer courses of chemotherapy without radiation therapy for those with advanced stage disease (Ansell 2018).

While centers may differ in their standard approach to treatment, ABVD (**Table 5**) is commonly used [as first treatment of HL] to initially treat favorable disease.

An alternative frontline regimen is escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone (escBEACOPP), which has shown a progression free survival (PFS) advantage over ABVD (**Table 6**). However, because of the unfavorable risk-benefit ratio of this regimen, such as an increased risk of severe acute toxicity and of secondary malignancies, the regimen is not universally used. As with any cancer-related treatment decision, the advantages and disadvantages of each regimen must be evaluated balancing risk with benefit for the individual patient.

Table 5. The ABVD Regimen in Hodgkin Lymphoma

	Dose	Days
Doxorubicin	25 mg/m² iv	1 + 15
Bleomycin	10 mg/m² iv	1 + 15
Vinblastine	6 mg/m² iv	1 + 15
Dacarbazine	375 mg/m² iv	1 + 15

Recycle: day 29
ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; iv, intravenous

Table 6. The escBEACOPP Regimen in Hodgkin Lymphoma

	Dose	Days
Bleomycin	10 mg/m² iv	8
Etoposide	200 mg/m² iv	1 to 3
Doxorubicin	35 mg/m² iv	1
Cyclophosphamide	1250 mg/m² iv	1
Vincristine	1.4 mg/m² iv[1]	8
Procarbazine	100 mg po	1 to 7
Prednisone	40 mg po	1 to 14
G-CSF	sc	From day 8

[1] Maximum absolute dose is 2 mg of vincristine
Recycle: day 22
escBEACOPP, bleomycin / etoposide / doxorubicin / cyclophosphamide / vincristine / procarbazine / prednisone in escalated dose;
G-CSF, granulocyte colonystimulating factor; iv, intravenous;
po, by mouth; sc, subcutaneous

Front-line treatment for limited-, intermediate- and advanced-stage disease

Limited/early disease

Stages I and II are considered limited disease. Combined-modality treatment consisting of a brief course of chemotherapy followed by radiotherapy was shown to result in superior tumor control compared with radiotherapy monotherapy (**Figure 2**) (Eichenauer 2018). There is debate of whether radiotherapy can be omitted in selected patients with complete metabolic response at interim PET, although available data consistently demonstrate a PFS advantage for patients treated with combined-modality despite a negative interim PET. Results of a Cochrane systematic review concluded that chemotherapy plus radiotherapy produces superior PFS over chemotherapy alone although adding radiotherapy to chemotherapy has little or no difference on OS (overall survival) (Blank 2017). In the RAPID clinical trial, patients with early stage, non-bulky HL with negative PET findings after 3 cycles of ABVD had a very good prognosis either with or without consolidation radiotherapy (Radford 2015). Currently, there is no consensus on a patient group that can be safely treated with chemotherapy alone.

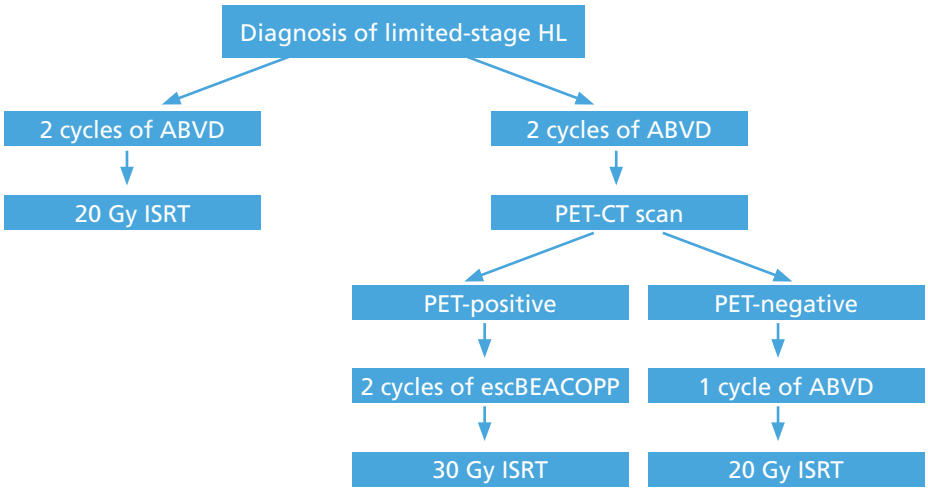

Figure 2. Therapeutic algorithm for newly diagnosed, limited-stage HL in patients ≤ 60 years The figure includes one approach not guided by interim PET based on a German Hodgkin Study Group study (left) and one PET-guided approach based on a EORTC study (right). ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; escBEACOPP, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/pro-carbazine/prednisone in escalated dose; ISRT, involved-site radiotherapy. Adapted from: Eichenauer 2018

Intermediate-stage disease

Intermediate-stage disease denotes early stage HL with risk factors such as the presence or absence of bulky disease and the presence or absence of B-symptoms. It is usually treated with combined modality approaches (**Figure 3**). Early treatment intensification appears to improve the prognosis of patients with a positive interim PET (a Deauville score ≥ 3).

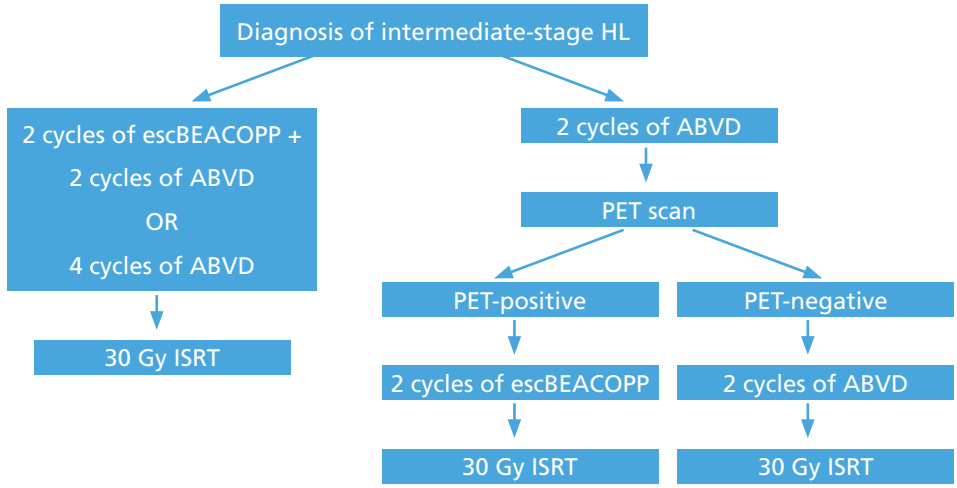

Figure 3. Therapeutic algorithm for newly diagnosed, intermediate-stage HL in patients ≤ 60 years The figure includes one approach not guided by interim PET based on a German Hodgkin Study Group study (left) and one PET-guided approach based on a EORTC study (right). ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; BEACOPPesc, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/pro-carbazine/prednisone in escalated dose; ISRT, involved-site radiotherapy. Adapted from: Eichenauer 2018

Advanced disease

Generally, stages III and IV HL are considered advanced disease although patients with stage IIB (stage II with B symptoms) have been included in two European clinical studies on treatment of advanced HL (Engert 2017; Johnson 2016a). According to a recent publication (Advani 2019), there are 2 strategies for initial therapy of advanced-stage HL: start with ABVD and then escalate or de-escalate based on interim PET imaging results, or start with escalated BEACOPP, perform an interim PET, then decide the next treatment step (**Figure 4**). The ABVD regimen, first described more than 40 years ago, yields cure rates of 70% to 80% similar to rates observed with more complex multidrug regimens (Johnson 2016a). The value of using PET-CT evaluation to guide treatment (described below) has allowed adaption of treatment intensity. For example, in the GSHG study (**Figure 4**), interim PET-CT negativity allowed a reduction to four cycles of escBEACOPP without compromising efficacy but with a reduction in treatment-related side effects (Borchmann 2017). In the RATHL study (**Figure 4**), bleomycin was omitted following interim negative PET-CT scan after two cycles of ABVD, leading to a lower incidence of pulmonary toxicity but not significantly lower efficacy (Johnson 2016a).

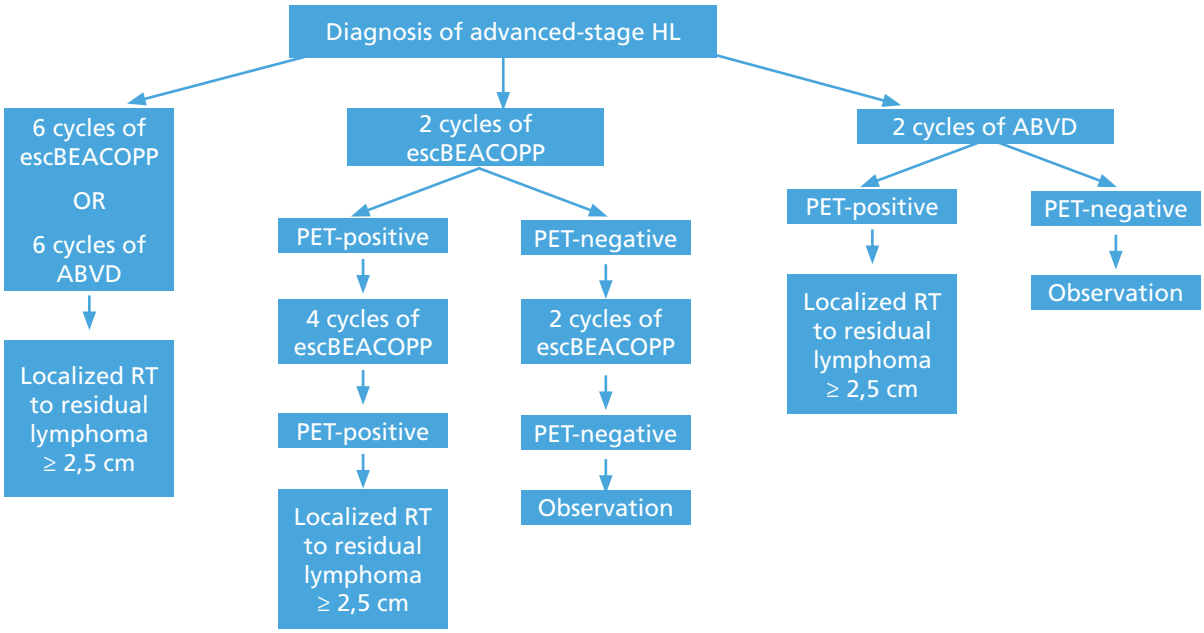

Figure 4. Therapeutic algorithm for newly diagnosed, advanced-stage HL in patients ≤ 60 years The figure includes one approach not guided by interim PET (left) and two PET-guided approaches based on the GHSG HD18 study (middle) (Borchmann 2017) and the RATHL study (right) (Johnson 2016a). ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; AVD, doxorubicin/vinblastine/dacarbazine; escBEACOPP, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose; CT, computed tomography; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; PET, positron emission tomography; RT, radiotherapy. Adapted from: Eichenauer 2018

The following are examples of individualized treatment schemas based on interim PET-adapted treatment strategies:
In three clinical trials, treatment started with 2 cycles of ABVD, then interim PET, followed by a switch to escalated BEACOPP for patients with PET-positive disease provided PFS rates ranging from 75% to 87% with an OS well above 90%. Patients with interim PET-positive disease had PFS rates between 60% and 65% (Press 2016; Johnson 2016b; Gallamini 2018).
Alternatively, start treatment with BEACOPP; patients with negative interim PET switch to ABVD and those with positive results remain on escalated BEACOPP. Results with this regimen are also very good, although outcomes in patients with positive PET results after 4 cycles of escalated BEACOPP were poor (Casanovas 2019).

Another treatment approach for advanced disease is brentuximab vedotin (BV) combined with AVD as frontline treatment. Primary prophylaxis with growth factor support (G-CSF) is recommended with BV-AVD.

The checkpoint inhibitors, nivolumab and pembrolizumab, are being investigated for frontline use in newly diagnosed patients with advanced cHL (Ramchandren 2019). Combination strategies of checkpoint inhibitors with conventional chemotherapy have shown effectiveness in relapsed/refractory cHL. Many unanswered questions about checkpoint inhibitors remain, such as defining the best modality for evaluation of response, confirming a strategy of modifying therapy based on the response, validating response endpoints specific to immune therapies and identifying predictive biomarkers for response (Khurana 2020).

Treatment for refractory/relapsed disease

Stem cell transplantation

Most patients with cHL are cured by first-line therapy, but significant percentages of patients (especially those with advanced disease) relapse or have primary refractory disease despite advances in combination chemo-radiotherapy and risk-adapted treatment escalation (Shanbhag 2018). Hematopoietic stem cell transplantation is the standard of care for patients with relapsed HL chemosensitive to salvage therapy; autologous stem cell transplantation (ASCT) in those without a prior autograft and allogeneic transplant (allo-SCT) in those after a failed prior autograft (Duarte 2019). Transplant provides significant improvements in outcomes compared with conventional chemotherapy alone and can lead to cure in approximately half of patients with relapsed or refractory disease (Majhail 2006).

Salvage treatment regimens such as dexamethasone/high-dose cytarabine/cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce tumor burden and mobilize stem cells before ASCT (Eichenauer 2018). Achievement of a negative PET should be the goal of salvage therapy as a complete metabolic response before high-dose chemotherapy and ASCT has been associated with an improved clinical outcome. Radiation therapy before ASCT may be useful in certain patients.

Relapse following ASCT generally occurs early (71% of event within 1 year of transplant, 90% within 2 years [Moskowitz 2015]). Patients with disease progression after ASCT uniformly have a poor outcome and treatment options are limited. Chemotherapy options include vinorelbine and gemcitabine for previously, heavily treated patients; the duration of response, however, is unfortunately short (Ansell 2018). Nivolumab, a human monoclonal PD-1-direted antibody, has demonstrated activity in patients with relapsed or refractory PD-1-positive HL following ASCT. Another treatment option is brentuximab vedotin. This treatment has been studied as a second-line therapy for relapsed/refractory HL, either sequentially or in combination with other regimens, also prior to ASCT (NCCN 2020).

Allo-SCT with myeloablative conditioning has been associated with lower relapse rates in patients with relapsed or refractory disease (NCCN 2020) and may control long-term disease recurrence via the graft-versus-lymphoma effect. Three-year relapse-free survival was 31% and 3-year OS as reported in a meta-analysis (Rashidi 2016). Transplant-related mortality is lower when the conditioning regimen is less intense and excellent outcomes have been shown with non-myeloablative allogeneic transplant using post-transplant cyclophosphamide (Eichenauer 2018). The anti-PD-1 agent nivolumab may induce a rapid onset of severe and treatment-resistant graft versus host disease (GvHD) if administered as treatment for relapsed disease after allogeneic transplant (Herbaux 2017; Haverkos 2017). And, while ipilimumab may be administered prior to allo-SCT, PD-1 inhibitors may increase the risk of acute GvHD post-transplant (Merryman 2017).

Immunotherapy

Another novel treatment for patients with multiple relapses are the anti-PD-1 agents nivolumab and pembrolizumab, which have been approved for treatment in this group of patients. Checkpoint inhibitors are not associated with the toxicities of traditional cytotoxic therapy but do carry a risk of autoimmune side effects related to a hyperactive T-cell response.

Palliative therapy with gemcitabine-based chemotherapy and/or regional radiation therapy may provide satisfying quality of life and prolonged survival in those patients with multiple relapses with no other treatment options.

Evaluation of Treatment Response

PET-CT is widely used not only in staging but also in response assessment at the end of therapy (see Module 1). Several studies have shown that a CR at interim PET scan after 2 to 4 cycles of ABVD is predictive of favorable outcomes independent of International Prognostic Score (IPS) risk group. Conversely, a positive interim FDG-PET after 2 cycles of treatment may result in intensification of therapy and a positive PET at the end of treatment may result in the addition of consolidation radiotherapy to the positive sites. A positive PET at any point may indicate the need for a repeat biopsy to confirm or exclude persistent disease (Ansell 2018).

PET treatment response assessment based on the Deauville 5-point scale [see Module 1] has prognostic value and is an important aspect of risk-adapted, individualized treatment strategies for early-stage HL (Barrington 2020).

Follow-up, Long-term Implications and Survivorship

The monitoring for secondary complications is of great importance in survivors of cHL. As the risk of relapse declines with time, the risk of death from cardiovascular disease and second malignancies increases. Newer treatment regimens, particularly reduced radiation doses and field size may lessen the risk of secondary complications: retrospective analyses indicate that both radiation therapy dose and field size, as well as intensity of chemotherapy (particularly alkylating agents and etoposide) correlate with an increased incidence of secondary malignancies (Swerdlow 2011). Despite less toxic treatment, patients with cHL have an enduring increased risk of death compared with the general population (Hapgood 2016). The following practices are recommended by the European Society of Medical Oncology (ESMO) for follow-up of patients:

- Follow-up should be conducted regularly to detect disease recurrence and therapy-related late effects
- History, physical examination and laboratory analysis should be carried out every 3 months for the first half year, every 6 months until the fourth year and once a year thereafter
- Thyroid function should be evaluated yearly if radiation was delivered to the neck area
- Testosterone and estrogen levels should be monitored, particularly in younger patients who received intensive chemotherapy
- Cancer screening should be conducted regularly after treatment due to an increased risk for the development of hematological and solid second malignancies
- Female patients who were ≤ 40 years at the time of chest or axillary irradiation should have a mammography yearly starting 8 to 10 years after radiation therapy. Those who were ≤ 30 years should have a breast MRI in addition to mammography (Eichenauer 2018)

Long-term effects of treatment and recommendations for follow-up in patients with lymphomas are discussed in detail in Module 4.

Future Perspective on treating Hodgkin Lymphoma

The use of PET as a tool for distinguishing response to therapy will continue to be investigated and further developed. In this light, two questions are in focus: will modification of therapy based on interim PET results allow for selection of patients for treatment escalation or de-escalation, and will these modifications improve outcomes (Advani 2019). New immunotherapeutic approaches for treatment of cHL being investigated include monoclonal CD30-specific antibodies, antibody-based radio-immunotherapy, antibody-based immunotherapy (such as brentuximab vedotin) and PD-1 blockading antibodies in combination with other established or novel therapies (Renner 2018). Similarly, new cellular therapies, such as the reprogramming of (autologous) T cells with CAR targeting the CD30 antigen is a promising approach as well as the combination of CD30-specific CAR T cells and PD-1 blocking antibodies (Renner 2018).

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Quick Facts

- Non-Hodgkin lymphomas vary from indolent to very aggressive, can be present in almost any part of the body and tend to be unpredictable in terms of their spread through the body, and are more common in older adults
- The two main subtypes of NHL, based on the cell line from which they develop, are B-cell lymphomas and T-cell lymphomas
- Diffuse large B-cell lymphoma (DLBCL) accounts for about one-third of all lymphomas, is aggressive and has numerous subtypes. T-cell lymphomas are relatively rare
- Patients may be asymptomatic at presentation and enlarged lymph nodes may be detected as an incidental finding; the presence of fever, night sweats and weight loss may or may not be prognostic of longer-term outcomes
- Watchful waiting is the standard of care during the initial encounter for patients with indolent types of NHL
- Standard therapy for untreated DLBCL is a 21-day schedule of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
- The usual therapy for aggressive nodal peripheral T-cell lymphoma is cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP), although favorable results have been obtained using CHOP + etoposide (CHOEP)

Overview of Non-Hodgkin Lymphoma (NHL)

Non-Hodgkin lymphoma (NHL) represents a wide and diverse range of cancers of the immune system that vary from the most indolent to the most aggressive malignancies, for which the extent of clinical resources are a major factor in assuring accurate diagnoses (Miranda-Filho 2019). NHL can be present in almost any part of the body, including the liver, bone marrow and spleen. In comparison to Hodgkin lymphoma, NHL is less predictable in terms of spread through the body, is infrequently localized at the time of diagnosis, frequently involves extranodal sites and has a poorer prognosis (Rademaker 2007).

Epidemiology and Pathogenesis

The estimated incidence of all types of NHL in Europe in 2018 was 18.5% with a mortality rate of 7.4% (all ages) (ECIS 2020). According to SEER data, there will be an estimated 77,240 new cases of NHL in the U.S. in 2020 representing 4.3% of all new cancer cases (SEER, 2020). Globally, the estimate of new cases of NHL in 2018 was 509,393 (2.8% of all cancers) with an estimated 248,724 deaths (2.6% of all cancer deaths) (Bray 2018).

While NHL can occur at any age, a large proportion of NHL diagnoses are in older age, with a peak incidence at ages 75 years and older (Cancer Research UK 2020; Miranda-Filho 2019). The relative frequency of specific subtypes of NHL varies geographically.

The two main subtypes of NHL, based on the cell line from which they develop, are B-cell lymphomas and T-cell lymphomas. About 85% to 90% of NHL are derived from B cells, the remaining lymphomas from either T cells or natural killer (NK) cells. The maturity of the B cell or T cell also dictates the type of lymphoma that develops. Some common types of B-cell lymphomas include:

- diffuse large B-cell lymphoma (DLBCL) (see below for a detailed description)
- Burkitt lymphoma
- chronic lymphocytic leukemia
- follicular lymphoma
- mantle cell lymphoma

Types of T-cell lymphoma include:

- peripheral T-cell lymphoma (PTCL) (see below for a detailed description)
- anaplastic systemic large cell lymphoma
- angioimmunoblastic lymphoma
- precursor T-lymphoblastic lymphoma/leukemia

Advances in next generation sequencing and gene-expression profiling techniques are contributing to current understanding of the pathogenesis of NHL. Similar to other types of cancer, the genetic lesions involved in NHL include activation of proto-oncogenes and disruption of tumor suppressor genes. The genome of lymphoma cells is relatively stable. Chromosomal translocations represent the main mechanism of proto-oncogene activation. These translocations are characterized by recurrence within a specific clinic-pathological category of NHL and are clonally represented in each tumor. The typical result of translocation is deregulated expression of a proto-oncogene (Evans 2003).

Factors possibly affecting the risk of developing NHL have been studied extensively. These factors include: immune disorders, medicines, infections, lifestyle, genetics, race, family history and occupational factors (Armitage 2017). Obesity has been found to be risk factor for DLBCL (Castillo 2014). Certain subtypes of NHL lymphomas (e.g., Burkitt lymphoma, MALT [mucosa-associated lymphoid tissue], splenic marginal zone) are associated with infections, including Epstein-Barr virus, Helicobacter pylori and hepatitis C virus. NHL is more common in patients who are immunosuppressed, such as patients with HIV/AIDS or recipients of an organ transplant.

Diffuse large B-cell lymphoma

Approximately 12.5% of hematological malignancies are diffuse large B-cell lymphoma (DLBCL) with DLBCL accounting for 30% to 35% of all lymphomas (SEER 2020). DLBCL is aggressive, growing quickly in the lymph nodes and often the spleen, liver, bone marrow or other organs with an estimated 5-year relative survival of 63.8% (2010-2016) and a 5.6 per 100,000 rate of new cases per year (SEER 2020).

DLBCL has numerous subtypes and some of these include high-risk histologies such as high-grade B-cell lymphomas not otherwise specified (NOS) and high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements, known as double (DHL) or triple hit (THL) lymphomas. Primary mediastinal B-cell lymphoma and transformed follicular lymphoma are less frequent, but important subtypes.

Identified risk factors for developing DLBCL include a family history of lymphoma, auto-immune disease, HIV, hepatitis C virus seropositivity, high body mass as a young adult and some occupational exposures (Morton 2014).

Peripheral T-cell lymphoma

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of tumors derived from the neoplastic transformation of mature (i.e., post-thymic) T lymphocytes or mature natural killer (NK) cells. PTCLs are rare and account for about 10% to 15% of all NHL (d'Amore 2015). The clinical, epidemiological, morphological, immunophenotypic, cytogenetic and molecular features of PTCLs are highly variable (Pizzi 2018); the most prevalent subtype is peripheral T-cell lymphomas not otherwise specified, which account for approximately 30% of all peripheral T cell cases. PTCLs are the least well understood form of NHL.

There appears to be a higher prevalence of PTCLs among Asian populations, probably due to the endemic occurrence of the Epstein-Barr virus (EBV). The male/female ratio is 2:1 and the median age at diagnosis is between 60 and 70, although both sex and age patterns vary according to different subtypes of PTCLs. Recurrent translocations, somatic mutations, host-tumor interactions, viral infections, dysregulation of signaling pathways, epigenetic regulatory patterns and/or metabolism are some of the factors that may be involved in the pathogenesis of peripheral T-cell lymphoma.

The World Health Organization (WHO) categorizes PTCL into three groups: nodal (about 60% of cases), extranodal (about 40% of cases) and leukemic, and as aggressive and indolent.

Classification of Non-Hodgkin Lymphomas

The classification schema for NHL is complex and ever evolving. The WHO classification scheme for lymphoma incorporates information from clinical findings, morphology, immunophenotyping and molecular genetics (Swerdlow 2016). This classification currently identifies 65 subtypes of NHL (see Appendix 1).

NHL is further classified by the aggressiveness of the disease. Categorizing NHL as low grade (indolent) or high grade (aggressive) is useful in determining the likely natural course and management of the disease (Al-Naeeb 2018).

Indolent NHL types have a relatively good prognosis although they are usually not curable in advanced clinical stages. Most patients with asymptomatic, indolent disease are managed with a "wait and watch" approach and may never require treatment (Ardeshna 2003). Early-stage (stages I and II) indolent NHL can be eventually effectively treated with radiation therapy alone. Low grade or indolent forms of lymphoma can, over time, change into a high-grade type. Most of the indolent types are nodular (or follicular) in morphology. In addition to follicular lymphoma, other types of low grade NHL include:

- Mantle cell
- Marginal zone
- Small lymphocytic/chronic lymphocytic leukemia
- Lymphoplasmacytic
- Cutaneous

Aggressive or high grade NHL tends to grow more quickly than low grade. A significant number of patients with aggressive type NHL can be cured with intensive combination chemotherapy regimens, which provide cure in about 50% of patients. The vast majority of relapses occur in the first 2 years after therapy. Diffuse large B cell lymphoma (DLBCL) is the most commonly occurring aggressive type of NHL. Other types include Burkitt lymphoma and peripheral T cell lymphoma.

Classification of T-cell lymphomas uses a framework based on the distinction between lymphocytes of the innate immune system, which are not antigen specific, versus those of the adaptive immune system, which are antigen specific (Armitage 2017). Relatively specific clinical features, morphological aspects, immunophenotypes and recurrent genetic alterations frequently characterize many of the distinct entities of T-cell lymphomas.

Refer to Module 1 for more information on classification schemas commonly used in lymphomas.

Initial Evaluation of Non-Hodgkin Lymphoma

Diagnosis

The diagnosis of NHL should be carried out in a reference hematopathology laboratory with expertise in morphological interpretation and the capacity to conduct the full range of phenotypic and molecular investigations required. No blood tests are specific for a diagnosis of NHL and results of routine blood examinations may be normal. An excisional lymph node biopsy is required for a definitive diagnosis. Workup should include laboratory assessment (CBC with differential, comprehensive metabolic panel, measurements of serum LDH levels) (NCCN 2020). Hepatitis B virus testing prior to initiation of treatment is recommended for patients who will receive anti-CD20 monoclonal antibody (MAB)-based regimens, measurement of uric acid, serum beta-2 microglobulin and hepatitis C testing may be useful (NCCN 2020) (**Table 1**).

Genetic features, detected by cytogenetics or fluorescence in situ hybridization (FISH) have become important in

defining specific NHL subtypes. The detection of viruses, particularly Epstein-Barr virus, HHV-8 (human herpesvirus 8, which is associated with all forms of Kaposi sarcoma) and HTLV1 (human T-cell leukemia virus) may be necessary to establish a specific diagnosis (NCCN 2020a).

Immunohistochemistry (IHC) is required for the differentiation of various subtypes of NHL to establish a diagnosis.

Expression of CD10 by either flow cytometry or immunochemistry must be determined for any B-cell lymphoma as this is a determining factor for distinguishing between several common B-cell lymphomas. Expression of CD30 should be considered in large B-cell lymphomas.

Discoveries advancing the understanding of genetic dysfunctions in large cell lymphomas have progressively refined diagnoses of DLBCL into more precise categories. Progress has been made to identify the subtypes of DLBCL based on either cell of origin or molecular and immunophenotypic features. Increasing understanding of the complex pathogenesis of DLBCL subtypes has led to efforts to target therapy with varying success; there is limited data to use disease subtype to differentiate therapy (Liu 2019).

In T-cell lymphomas, information on T-cell receptor genes and the cell of origin play an important role in both tumor biology and clinical behavior thus underscoring the clinical relevance of this information in the light of an increasing number of targeted therapeutic options (d'Amore 2015).

Refer to Module 1 for more information on the diagnostic procedures commonly used in lymphomas.

Table 1. Essential and Useful (under certain conditions) Diagnostic Workup Procedures in NHL

Essential procedures and tests:	History and physical exam Performance status Assessment of B symptoms Complete blood count, blood chemistry including lactate dehydrogenase (LDH), uric acid, Hepatitis B testing[1] Excisional or incisional biopsy of node/lymphoma Adequate immunophenotyping to establish diagnosis PET/CT whole body Karyotype or FISH Calculation of International Prognostic Index (IPI) score
Useful procedures and tests:	Molecular analysis to detect clonal T-cell antigen receptor (TCR) [2] HIV, hepatitis C testing CT of neck and head EBV testing[2] Echocardiogram (if anthracycline chemotherapy indicated) Bone marrow biopsy (in certain cases) Lumbar puncture (if CNS disease suspected)

[1]diffuse large B-cell lymphoma; [2]peripheral T-cell lymphoma
CNS, central nervous system; FISH, fluorescence in situ hybridization
Sources: d'Amore 2015; NCCN 2020a; NCCN 2020b; Tilly 2015

Clinical manifestations

NHL can involve any organ in the body, a multitude of presentations is possible and symptoms might mimic a wide range of other conditions (Armitage 2017). Lymphadenopathy, in which a single lymph node or several nodes may be enlarged, or splenomegaly are commonly found at initial presentation. The swelling develops over months or years in low-grade lymphoma but at a much faster rate in high-grade lymphoma. Almost one-third of patients have extranodal disease in which almost any organ or tissue can be involved.

In NHL, involved lymph nodes can be

- Contiguous: affected lymph nodes are adjacent to each other, or
- Noncontiguous: affected lymph nodes are not adjacent to each other but are on the same side of the diaphragm

The presence of B-symptoms (fever, night sweats, weight loss) as signs of disseminated disease may, but do not necessarily, confer an unfavorable outcome in NHL. Patients may be asymptomatic at presentation and in some cases enlarged lymph nodes are detected as an incidental finding. A singular, solid extranodal tumor may mimic other forms of cancer.

Tumor bulk

In contrast to defined sizes of nodes to establish tumor bulk in Hodgkin lymphoma, there is a lack of conformity on node size in establishing tumor bulk in NHL. In DLBCL, 6 to 10 cm is a node size commonly used to refer to bulk.

Staging and Risk Assessment

As applies generally to all lymphomas, PET-CT with FDG is the imaging technique preferred for staging NHL due to its higher sensitivity than CT alone. In DLBCL, PET leads to upstaging for approximately 15% of patients (El-Galaly 2018).

Timing of pretreatment baseline scans should be based on the clinical situation. For aggressive lymphoma, such as DLBCL, scans within 4 weeks would be appropriate.

The Ann Arbor Staging System (**Table 2**) is the most common system used for classifying most subtypes of NHL. The system is based on where the disease is located in the body. Refer to Module 1 for general information on staging schemas used in lymphomas.

Table 2. Ann Arbor Staging System

Stage I	Involvement of a single lymph node or lymph node region or, involvement in an organ or site other than a lymph node (extranodal) but without spread to other organs or lymph nodes
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm
Stage IIE	Localized involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm
Stage III	Involvement of lymph node regions on both sides of the diaphragm, with or without partial involvement of an extranodal organ or site above or below the diaphragm
Stage IV	Widespread disease, including multiple involvements in one or more extranodal sites, such as the bone marrow

Source: Tilly 2015

The presence or absence of disease-related symptoms of fevers, unexplained weight loss or drenching night sweats does not appear to correlate with outcome in any of the commonly used prognostic scores in NHL. The prognosis of DLBCL is based on clinical, molecular and genetic factors as well as responsiveness to induction therapy (Jain 2019).

The risk assessment of NHL often relies on prognostic scores derived from simple clinical information. Several systems for predicting prognosis and making a treatment recommendation have been developed for NHL. The most prominent example of a clinical prognostic score is the International Prognostic Index (IPI), which was developed for aggressive B-cell and T-cell lymphomas but is predictive in essentially all subtypes of NHL (Armitage 2017). The IPI is based on five individual risk factors (**Table 3**). Prognostic indexes have been developed for follicular lymphoma (FLIPI) and for mantle cell lymphoma (MIPI).

Table 3. The International Prognostic Index (IPI)	
Risk factors (all patients) (1 point for each factor present)	Age > 60 years Serum LDH higher than the highest normal value Stage 3 or 4 ECOG performance status 2–4 Extranodal sites in 2 or more sites
Risk categories	Low (0 or 1 points) Low-intermediate (2 points) High-intermediate (3 points) High (4–5 points)
Risk factors (patients ≤60 years) (1 point for each factor present)	Serum LDH higher than the maximum normal value Stage 3 or 4 ECOG performance status 2–4
Risk categories	Low (0 points) Low intermediate (1 point) High intermediate (2 points) High (3 points)
ECOG, Eastern Cooperative Oncology Group; LDH, serum lactate dehydrogenase Adapted from: Zhou 2014	

Extranodal disease and disease stage are essential components of the IPI scoring system emphasizing the importance of using sensitive imaging techniques such as PET-CT. While several tools are available to determine prognosis in NHL, the IPI is most commonly recommended in professional practice guidelines such as those developed by the NCCN and ESMO.

Treatment

Treatment considerations in Non-Hodgkin Lymphoma

Generally, watchful waiting (sometimes referred to as active surveillance) is the standard of care during the initial encounter for patients with indolent types of NHL (e.g., follicular lymphoma, lymphoplasmacytic lymphoma) (**Table 4**). A biopsy may be performed in patients who experience a relapse to identify the histology of the lymphoma. Conversion to a more aggressive histology often requires a change in the plan and type of therapy.

Table 4. Overview of Treatment Options for Selected Types of Indolent NHL

Type	Presentation	Initial treatment	Treatment of progressive/ relapsed disease
Follicular lymphoma	Widespread nodal involvement, splenic/bone marrow involvement; rearrangement of BCL2 gene	Stage 1 & 2: watchful waiting, radiation, rituximab Stage 2 (enlarged lymph nodes) & 3: watch and wait; radiation to affected nodes; Symptomatic disease: rituximab or obinutuzumab + chemotherapy; targeted therapy; lenalidomide; immunotherapy	Watchful waiting if advanced asymptomatic disease; repeat rituximab + chemotherapy; bendamustine + obinutuzumab; radio-immunotherapy; autologous/allogeneic transplant may be considered
Lymphoplasmacytic lymphoma/ Waldenström macroglobulinemia	Bone marrow/splenic/lymph node involvement; hyperviscosity syndrome possible	Monitor; plasmapheresis (possible); rituximab ± ibrutinib; nucleoside analogs; R-CHOP	Autologous/allogeneic hematopoietic stem cell transplant in selected cases
Marginal zone lymphoma Gastric MALT (also called extranodal) Splenic marginal zone lymphoma Nodal	 Frequent history of autoimmune disease; lesions in stomach Splenomegaly, peripheral blood/ bone marrow involvement Disseminated lymphadenopathy with/ without blood/bone marrow involvement; B symptoms	 Antibiotics for underlying Helicobacter pylori; watchful waiting Watchful waiting; splenectomy; rituximab ± purine analogs or alkylating agents Watchful waiting; radiation therapy; rituximab + bendamustine; rituximab + cyclophosphamide + vincristine + prednisone (R-CVP)	 Radiation therapy; chlorambucil, bendamustine, rituximab, lenalidomide Ibrutinib; lenalidomide
Cutaneous T cell	Develop primarily in skin, may become systemic; wide spectrum of subtypes	Topical therapies with ultraviolet light/ electron beam therapy; radiation therapy for localized disease; watchful waiting; doxorubicin-based combination chemotherapy for disseminated disease	Romidepsin; vorinostat; mogamulizumab; brentuximab vedotin

MALT, gastric mucosa-associated lymphoid tissue; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride (Hydroxydaunomycin), vincristine sulfate (Oncovin), prednisone
Sources: Leukemia & Lymphoma Society 2020; McNamara 2020; Zucca 2020

The 5-year survival for adult patients diagnosed with NHL is 72.7% (2010-2016 data, SEER 2020), although there is wide variation in survival according to disease subtype. Treatment strategies should be adapted according to factors such as subtype, IPI score and co-morbidities. Inclusion in a clinical trial, whenever possible, should be strongly considered.

Treatment of diffuse large B-cell lymphoma

Front-line treatment

Because of the aggressive nature of diffuse large B-cell lymphoma (DLBCL) and the typical presentation of patients with rapidly enlarging lymphadenopathy and constitutional symptoms, immediate treatment is warranted (Liu 2019). Standard therapy for untreated DLBCL remains a 21-day schedule of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (NCCN 2020a), with long-term remissions reported in clinical trials to be up to two-thirds of patients (Ayers 2020). R-CHOP may be followed by involved site radiation therapy for patients with or without non-bulky disease (NCCN 2020a). Dose intensity of the R-CHOP regimen may change commensurate with the patient's age and overall physical state and disease stage. Increasingly, evidence indicates that DLBCL consists of many subtypes that are not all optimally treated by one approach.

High-dose therapy and autologous stem cell rescue as consolidation therapy for patients in first complete remission after induction therapy has no apparent benefit over R-CHOP and is therefore not routinely recommended.

Patients who have high-risk features, such as cytogenetic abnormalities, bulky disease or those diagnosed with high-grade B-cell lymphoma, may experience poor outcomes when treated with standard R-CHOP frontline.

Alternative frontline treatment for these patients is intensive immunochemotherapy such as dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R); rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine (R-HyperCVAD); or rituximab, cyclophosphamide, vincristine, doxorubicin and high-dose methotrexate alternating with ifosfamide, etoposide and cytarabine (R-CODOX/M-IVAC) in investigational as well as standard-of-care settings (Ayers 2020). A recent clinical trial, however, found a lack of a survival benefit with DA-EPOCH-R versus R-CHOP with a significantly higher incidence of grade ≥ 3 adverse events in the DA-EPOCH-R group (Bartlett 2019).

Patients with high-intermediate and high-risk IPI, especially those with more than one extranodal site or elevated lactate dehydrogenase (LDH) and age > 60 years are at higher risk of central nervous system (CNS) relapse. CNS involvement tends to occur early, either during systemic chemotherapy or shortly after its completion (McKay 2020). The optimal method of administering prophylactic treatment with high-dose methotrexate, intrathecal versus intravenous, has become a point of debate with the advent of rituximab therapy and there is no strong evidence that prophylactic treatment prevents CNS relapse risk. Should there be an indication for CNS prophylaxis, high-dose intravenous methotrexate administered as early as possible as part of first-line therapy is recommended (McKay 2020).

Treatment for refractory/relapsed disease

At the time of progression or disease relapse, the standard treatment for transplant eligible patients remains salvage chemotherapy followed by consolidative autologous stem cell transplant (Liu 2019) as a curative-intent treatment in patients with chemosensitive disease (Ayers 2020). In patients < 65 to 70 years with good performance status and no major organ dysfunction, ESMO recommends rituximab and chemotherapy followed by high-dose chemotherapy and autologous transplant (Tilly 2015). The potential toxicities of regimens need to be considered. Patients not suitable for high-dose therapy may be treated with the same or other regimens such as R-GEMOX (rituximab, gemcitabine, oxaliplatin).

Chimeric antigen receptor T-cell therapy (CAR-T) plays an increasingly important and evolving role in treating patients with refractory/relapsed disease (Liu 2019). Axicabtagene ciloleucel and tisagenlecleucel are FDA-approved for the treatment of adult patients with relapsed/refractory DLBCL, high-grade B-cell lymphomas and in cases of histologic transformation of follicular lymphoma to DLBCL in patients who have failed two or more prior systemic therapy regimens (Zelenetz 2019). These CAR-T agents should only be dispensed and administered in healthcare facilities with appropriate support services. Research in this therapy area as well as other novel therapeutics is currently ongoing.

Treatment of nodal peripheral T-cell lymphoma

Front-line treatment

The prolific number of subgroups of peripheral T-cell lymphomas makes running clinical trials difficult and means that treatment guidelines are often based on expert opinion (Armitage 2017). Cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin) and prednisone (CHOP), or some variant, is the most commonly used regimen in aggressive nodal peripheral T-cell lymphoma (d'Amore 2015). CHOP + etoposide (CHOEP) provided higher complete response rates than CHOP (88% vs 79%, respectively) in patients ≤ 60 years of age in one older European study (Pfreundschuh 2004). This regimen, followed by autologous stem cell transplant in chemosensitive and transplant-eligible patients provides good overall and progression-free survival outside of a clinical trial (d'Amore 2015).

Several of the peripheral T-cell lymphoma subtypes express CD30. Significant improvement in progression-free survival and overall survival (OS) was demonstrated with initial treatment with brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone versus standard therapy (CHOP) for patients with CD30-positive peripheral T-cell lymphoma (Horwitz 2019). Results of this clinical trial support the potential of this new regimen (A+CHP) to become a new standard therapy for these patients.

Treatment for refractory/relapsed disease

Unfortunately, the treatment response duration is often short and relapses are frequent in this population. Brentuximab vedotin (BV) is the only globally approved salvage treatment and there is no standard of care for relapsed/refractory nodal peripheral T-cell lymphoma (d'Amore 2015). Other treatment options include combination chemotherapy such as DHAP (dexamethasone, high-dose cytarabine, cisplatin) or ICE (ifosphamide, etoposide, carboplatin) in chemosensitive patients followed by allogeneic stem cell transplant in fit, eligible patients or allogeneic transplant using myeloablative conditioning or reduced-intensity conditioning (NCCN 2020b). A summary of research findings indicated that the durability of benefit using high-dose therapy followed by autologous transplant was less than that achieved with allogeneic transplant in patients with refractory/relapsed disease (NCCN 2020b).

Radiotherapy

Peripheral T-cell lymphomas tend to be somewhat less radiosensitive than the aggressive B-cell lymphomas. Therefore, higher radiation doses may be needed if radiotherapy is planned. Palliative radiotherapy may be used to treat locally symptomatic disease.

Evaluation of Treatment Response

In most treatment centers, an end-of-treatment PET-CT scan is performed to assess efficacy of treatment and thus complete remission and predict disease-free survival. The results of the scan are evaluated using the 5-point Deauville score [see Module 1]. Interim restaging is conducted after 1 to 3 cycles of chemotherapy. These repeated staging studies assist in treatment decisions related to what, when and how much subsequent therapy is appropriate.

Follow-up, long-term implications and survivorship

There is no conclusive evidence that surveillance imaging can improve survival in NHL (Armitage 2017). The focus of follow-up should be placed on survivorship issues.

Pelvic radiation therapy and large cumulative doses of cyclophosphamide have been associated with a high risk of permanent sterility. For as long as 30 years after diagnosis, patients are at a significantly elevated risk of developing second primary cancers, especially those at certain sites:

- Lung
- Brain
- Kidney
- Bladder
- Melanoma
- Hodgkin lymphoma
- Acute non-lymphocytic leukemia

Detailed information on follow-up and assessment of long-term complications and their associated nursing interventions is discussed in Module 4.

Future Perspective on treating Non-Hodgkin Lymphoma

Technology and knowledge are steadily evolving to aid understanding the unique pathogenesis of each subtype of NHL. Advances in bioinformatics and gene-editing technologies in translational medicine will eventually lead to significant progress in identifying mutations, which can be translated into therapeutic targets (Liu 2019). Targeted therapy will, in the future, make a difference in outcomes, especially in patients who have refractory disease or who have relapsed.

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Appendix 1: Classification of Non-Hodgkin Lymphoma Subtypes[1]

Mature B-cell neoplasms:
• Chronic lymphocytic leukemia and small lymphocytic lymphoma • Monoclonal B-cell lymphocytosis • B-cell prolymphocytic leukemia • Splenic marginal zone lymphoma • Hairy cell leukemia • Unclassifiable splenic B-cell lymphoma or leukemia[2] • Splenic diffuse red pulp small B-cell lymphoma[2] • Hairy cell leukemia variant • Lymphoplasmacytic lymphoma • Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue • Nodal marginal zone lymphoma • Pediatric nodal marginal zone lymphoma[2] • Follicular lymphoma • In-situ follicular neoplasia • Pediatric-type follicular lymphoma • Large B-cell lymphoma with rearrangement of IRF4[2] • Primary cutaneous follicle center lymphoma • Mantle cell lymphoma • In-situ mantle cell neoplasia • DLBCL, NOS • T-cell rich or histocytes-rich large B-cell lymphoma • Primary DLBCL of the CNS • Leg-type primary cutaneous DLBCL • EBV-positive DLBCL, NOS • EBV-positive mucocutaneous ulcer[2] • 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 • Primary effusion lymphoma • Human herpesvirus 8-positive DLBCL, NOS[2] • Burkitt lymphoma • Burkitt-like lymphoma with chromosome 11q aberrations[2] • High-grade B-cell lymphoma with rearrangements of BCL2 and MYC or of BCL6 and MYC[2] • High-grade B-cell lymphoma, NOS[2] • Unclassifiable B-cell lymphoma with features that are intermediate between DLBCL and classic Hodgkin lymphoma

[1] Plasma cell neoplasms, Hodgkin lymphomas, post-transplant lymphoproliferative disorders and tumors of histiocytic and antigen-present cells are not included in this list. [2] Provisional entities
CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein Barr virus; NOS, not otherwise specified
Adapted from: Armitage 2017

Mature T-cell and natural killer (NK)-cell neoplasms:
• T-cell prolymphocytic leukemia • T-cell large granular lymphocytic leukemia • Chronic lymphoproliferative disorder of NK cells[2] • Aggressive NK-cell leukemia[2] • EBV-positive T-cell lymphoproliferative diseases of childhood • Adult T-cell leukemia or lymphoma • Nasal-type extranodal NK-T-cell lymphoma • Enteropathy-associated T-cell lymphoma • Monomorphic epitheliotropic intestinal T-cell lymphoma • Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract[2] • Hepatosplenic T-cell lymphoma • Subcutaneous panniculitis-like T-cell lymphoma • Mycosis fungoides • Sezary syndrome • Primary cutaneous CD30-positive T-cell lymphoproliferative disorders • Lymphomatoid papulosis • Primary cutaneous anaplastic large cell lymphoma • Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma[2] • Primary cutaneous acral CD8-positive T-cell lymphoma[2] • Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder[2] • Peripheral T-cell lymphoma, NOS • Angioimmunoblastic T-cell lymphoma • Follicular T-cell lymphoma[2] • ALK-positive anaplastic large cell lymphoma • ALK-negative anaplastic large cell lymphoma • Breast-implant-associated anaplastic large cell lymphoma[2]
[1] Plasma cell neoplasms, Hodgkin lymphomas, post-transplant lymphoproliferative disorders and tumors of histiocytic and antigen-present cells are not included in this list. [2] Provisional entities CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein Barr virus; NOS, not otherwise specified Adapted from: Armitage 2017

Quick Facts

- Bleomycin should be used with caution in patients with compromised pulmonary function due to the high risk of severe and life-threatening pulmonary toxicity
- Cytokine release syndrome can occur with some types of immunotherapy such as bispecific monoclonal antibodies and CAR T-cells
- Despite advances in the dosing and administration of radiation therapy, common side effects such as radiation dermatitis and nausea and vomiting can occur, depending on the area of the body being treated
- Because of the long-term sequela of treatment, patients need to be informed about and comply with the need for regular medical checkups
- The incidence of secondary malignancies increases as time past treatment elapses requiring stringent follow-up and patient education on this risk
- Cardiovascular disease following lymphoma treatment is the leading non-cancer-related cause of death in lymphoma survivors

A. Management of the Side Effects of Lymphoma and Lymphoma Treatment
    1. Side effects of systemic treatment
    2. Common problems experienced before, during and immediately following treatment
    3. Side effects of radiation therapy
B. Management of the Patient undergoing Hematopoietic Stem Cell Transplant
C. Support and Facilitation of Shared Decision-making
    1. Components
    2. Patient/healthcare professional factors in shared decision-making
    3. Implementation strategies
D. Cancer Survivorship
    1. Health-related quality of life
        i. Cognition
        ii. Emotional changes
        iii. Sexuality
        iv. Coping strategies
    2. Fertility and family planning
E. Follow-up Care
    1. Post-treatment period
    2. Longer-term follow-up

References

Management of the Side Effects of Lymphoma Treatment

Side effects of systemic treatment

In regard to all medications and chemotherapeutic agents administered, both patients and their caregivers should be provided information on:

- mechanism of action
- route and duration of administration
- possible and expected side effects
- self-care measures

The side effects of systemic agents commonly used to treat lymphomas and the associated nursing- and patient measures to prevent or manage these effects are presented in **Tables 1** and **2**. There are some agents that, because of either their mode of action or adverse effects with a potential to be life threatening, require special mentioning. These are as follows:

Bleomycin should be used with caution in patients with compromised pulmonary function, compromised renal function, those receiving concomitant chest radiation, concomitant administration of cisplatin, cyclophosphamide, methotrexate or doxorubicin, those older than 40 years of age and the use of granulocyte-colony stimulating factor (G-CSF) during treatment (NCCN 2020; Andersen 2019). These risk factors may predispose the patient to bleomycin pulmonary toxicity, which can be severe and life threatening.

Co-administration of **brentuximab vedotin** and bleomycin may increase the risk of pulmonary toxicity; bleomycin should be discontinued prior to starting brentuximab vedotin treatment (Seattle Genetics 2012). Peripheral neuropathy is usually sensory in nature, but motor neuropathy has been reported. Peripheral neuropathy is dose-cumulative and usually occurs several months into therapy. Symptoms usually subside in about 7 weeks, but patients may have residual symptoms, which include hypoesthesia, hyperesthesia, paresthesia, discomfort, burning sensation, neuropathic pain or weakness. These symptoms may require dose modifications or discontinuation. Severe infusion-related reactions can occur and present as wheezing, difficulty breathing, hives, itching and swelling. If a reaction occurs, the infusion should be immediately and permanently discontinued and appropriate medical management instituted (Seattle Genetics 2012). Patients with rapidly proliferating tumor or high tumor burden may be at increased risk for the development of tumor lysis syndrome following brentuximab vedotin administration.

Methotrexate should be administered with caution in older patients due to an increased risk for toxicity due to decreased hepatic and renal function as well as decreased folate stores. A dose reduction and monitoring for early signs of toxicities is advisable (Mayne Pharma 2003). Leucovorin is required in some methotrexate regimens (usually following methotrexate doses > 500 mg/m^2) to selectively "rescue" normal cells from the adverse effects of methotrexate caused by inhibition of production of reduced folates.

Ifosfamide-induced encephalopathy can occur from 1 to 4 days after administration and may persist from 1 to 30 days. Most cases are reversible. Nonspecific symptoms include extrapyramidal symptoms, fecal/urinary incontinence, seizures, somnolence, confusion, amnesia, depressive psychosis, hallucinations and other psychiatric disturbances. Symptom severity can range from mild somnolence or agitation to hallucinations to deep coma. Encephalopathy may be dose-dependent; risk increases with shorter infusion times. To decrease the incidence and severity of bladder toxicity, assure adequate hydration with attention to fluid balance, and administration of mesna, a uroprotective agent, if needed. Urine should be examined for the presence of erythrocytes, which may precede hemorrhagic cystitis.

While still investigational in some cancers, chimeric antigen receptor T-cell therapy (CAR-T), which involves the alteration of a patient's T cells so that they kill cancer cells, provides promising outcomes in the treatment of lymphomas and has been approved for treatment of DLBCL. Unique to CAR-T treatment is the incidence of cytokine release syndrome, a serious immune-related adverse event, which can be life threatening if not identified and treated early (see below for management). Another significant complication of CAR T-cell therapy is the immune effector cell-associated neurotoxicity syndrome (ICANS). This syndrome presents a continuum from mild tremor to cerebral edema and in a minority of cases, death. To insure patient safety, it is imperative that CAR T-cell therapy be administrated in a setting in which healthcare professionals are knowledgeable about administration and side effects and can provide high-quality care.

Table 1. Side Effects of Agents commonly used in Treating Lymphomas and Their Nursing Management

Drug/Class/Route	Potential side effects	Nursing Management
Bendamustine Alkylating agent IV	Infusion-related reactions; myelosuppression; GI symptoms (anorexia, constipation, diarrhea, nausea/vomiting, stomatitis); fatigue; injection site reactions; skin reactions (rash)	Consider premedication for infusion reactions; Assess for infusion reactions (fever, chills, pruritus, rash) during or directly after infusion; Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding, preventative measures and when to contact HCP
Bleomycin Antitumor antibiotic IV	(See above); rash, pneumonitis; febrile reactions; infusion-related reactions	Premedication with hydrocortisone or antipyretics or antihistamines to prevent febrile reactions; Educate patient on signs/symptoms of pulmonary fibrosis (dry, unproductive cough or dyspnea on exertion)
Brentuximab vedotin Antibody-drug conjugate IV	(See above). Peripheral neuropathy; infusion-related reactions; anemia, neutropenia, thrombocytopenia	Premedication to prevent possible infusion-related reactions (chills, nausea, dyspnea, pruritus, pyrexia, cough); Provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding, preventative measures and when to contact HCP
Corticosteroids (dexamethasone, prednisone) Oral	Fatigue, thinning of skin, adrenal insufficiency, hyperglycemia, increased risk of infection, leukocytosis, bone thinning, osteoporosis, mood swings, personality changes, weight gain, decreased libido	Monitor for hyperglycemia/hypoglycemia; Educate patients on side effects including increased infection risk, signs/symptoms of infection, preventative measures and when to contact HCP. Instruct not to abruptly stop taking corticosteroids
Cyclophosphamide Alkylating agent Oral	Cardiac dysfunction (dose-related); nausea/vomiting; myelosuppression; hemorrhagic cystitis; hyperuricemia; infertility; secondary malignancies	Provide prophylactic antiemetics; monitor for transient ECG changes, dyspnea, tachypnea, fluid retention; encourage fluid intake; educate patient on increased infection risk, signs/symptoms of infection and preventative measures; monitor for signs/symptoms of TLS; Longer term monitoring for secondary malignancies; refer to fertility specialist
Cytarabine (also known as arabinofuranosyl cytidine [ARA-C]) Antimetabolite IV	Myelosuppression; skin rash; GI upset; neurotoxicity; sepsis, infections with high dose; nausea, vomiting; cytarabine syndrome (flu-like symptoms); TLS	Monitor for allergic reaction, seizures, loss of consciousness; provide antiemetics as needed; provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding, preventative measures and when to contact HCP
Dacarbazine Alkylating agent IV	Leukopenia, thrombocytopenia; nausea/vomiting/anorexia; hepatotoxicity; facial flushing, tingling sensations	Prophylactic administration of antiemetics; Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, preventative measures and when to contact HCP; monitor hepatic function during therapy; some patients may require increased dilution
Doxorubicin (Hydroxydaunorubicin) Anthracycline IV	Nausea, vomiting; fatigue; alopecia; stomatitis; sensitivity to sunlight; watery eyes, loss of fertility	Administration of pharmacologic interventions for prophylaxis of nausea/vomiting (benzodiazepines), for acute nausea/vomiting (5-HT3 receptor antagonists, dexamethasone, aprepitant, benzodiazepine); hold ice chips in cheeks or suck on ice chips/ice cold water during administration; assess cardiac status before drug initiation; provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding, preventative measures and when to contact HCP; referral to fertility specialist
Etoposide Plant alkaloid Oral	Neutropenia, thrombocytopenia; alopecia; nausea/vomiting, stomatitis, diarrhea; hypotension; radiation recall	Provide antiemetic as needed; educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, preventative measures and when to contact HCP
Everolimus mTORC1 inhibitor Oral	Immunosuppression; high potential for drug-drug interactions; diarrhea, stomatitis; fatigue; hypersensitivity reaction	Provide education on increased infection risk, signs/symptoms of infection, preventative measures and when to contact HCP; review use of concomitant medications; encourage use of topical, systemic or intra-lesional corticosteroids for stomatitis relief

Table 1. Side Effects of Agents commonly used in Treating Lymphomas and Their Nursing Management

Drug/Class/Route	Potential side effects	Nursing Management
G-CSF/filgrastim Cytokine SC	Joint, bone pain; elevated WBCs; pyrexia, elevated serum alkaline phosphatase; headache	Assess and medicate for pain/discomfort
Ifosfamide Alkylating agent IV	(See above); Leukopenia, thrombocytopenia; nausea/vomiting; hemorrhagic cystitis, hematuria; encephalopathy	Contraindicated in presence of severe leukopenia, thrombocytopenia, severe renal and/or hepatic impairment, active infections, advanced cerebral arteriosclerosis; assess for symptoms of encephalopathy; administer antiemetics; Advise on signs/symptoms of hematuria and benefit of adequate hydration; provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding, preventative measures and when to contact HCP
Lenalidomide Immunomodulator	Diarrhea, constipation, nausea; anemia, fatigue; neutropenia, thrombocytopenia; peripheral edema; insomnia; muscle cramps, spasms, back pain; pyrexia; upper respiratory tract infection; skin rash; dyspnea; dizziness; tremor; thromboembolic event in combination with steroids	Monitor CBC; provide education on increased infection & bleeding risk, signs/symptoms of infection & bleeding, preventative measures and when to contact HCP; monitor GI status; thromboembolism prophylaxis; assess skin for changes
Methotrexate Antimetabolite IV, IM, IT, Oral	Neutropenia, thrombocytopenia; stomatitis; vomiting; hepatotoxicity; azotemia (more common with high dose), hyperuricemia; neurotoxicity, pulmonary toxicity; renal dysfunction	Dose adjustments may be necessary in patients with hepatotoxicity or myelosuppression or in elderly patients; monitor for signs/symptoms of infection and bleeding; monitor renal function; educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, preventative measures and when to contact HCP
Procarbazine Alkylating agent Oral	Myelosuppression; nausea/vomiting; loss of fertility; secondary malignancies	Educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, preventative measures and when to contact HCP; longer term monitoring for secondary malignancies (lung cancer, AML)
Rituximab (Anti CD20) Monoclonal antibody IV	Fever, chills; weakness; nausea; headache; cough; cold symptoms	Because of a risk of viral reactivation, patients should be screened for hepatitis B before administration; attenuates response to vaccines for up to 6 months; positive response indicators include: female gender, age <40 years, shorter period between diagnosis and rituximab administration; may cause temporary low BP; advise patient to contact HCP if any side effects become severe
Vinblastine Mitotic inhibitor Vinca alkaloid IV	Leukopenia (dose-related); neurotoxicity (central and peripheral), increased risk with higher doses/prolonged administration; constipation; TLS; acute shortness of breath; ototoxicity; risk of secondary malignancy	Initiate recommended procedures to prevent drug extravasation; educate patient on signs/symptoms of drug extravasation; educate on measures to prevent sunburn; educate on measures to prevent and recognize infection; educate patients on side effects including signs/symptoms of peripheral neuropathy and when to contact HCP; administer stool softeners/laxatives prophylactically to prevent constipation
Vincristine Plant alkaloid IV	Vesicant; alopecia; constipation; peripheral/central neuropathy; hyperuricemia due to cell lysis	Initiate recommended procedures to prevent drug extravasation; educate patient on signs/symptoms of drug extravasation; educate patients on side effects including signs/symptoms of peripheral neuropathy; and when to contact HCP. Administer stool softeners/laxatives prophylactically to prevent constipation

AML, acute myelogenous leukemia; CBC, complete blood count; ECG, electrocardiogram; GI, gastrointestinal; HCP, healthcare professional; IM, intramuscular; IT, intrathecal; IV, intravenous; SC, subcutaneous; TLS, tumor lysis syndrome
Sources: NCCN 2019; http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index

Table 2. Side Effects of Agents Currently under Investigation for Treating Lymphomas and Their Nursing Management

Drug/Class/Route	Potential side effects	Nursing Management
CAR T cell	Cytokine-release syndrome (can range from mild to severe); neurologic toxicities; TLS; B-cell aplasia	Should be administered by knowledgeable staff; monitor temperature, vital signs; administer acetaminophen, narcotics, antiemetics as needed; monitor lab values; assess for neurologic symptoms; provide allopurinol and hydration; educate patients on side effects including increased infection risk, signs/symptoms of infection, preventative measures and when to contact HCP
Gemcitabine Antimetabolite IV	Anemia, neutropenia, thrombocytopenia; hemolytic uremic syndrome (infrequent but may result in renal failure); elevated liver enzymes (transient/reversible); flu-like symptoms; severe pulmonary toxicity; skin rash (mild/moderate)	Monitor renal/liver function; acetaminophen for relief of flu-like symptoms; apply corticosteroids for skin rash; educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, preventative measures and when to HCP
Ibrutinib Molecular targeted therapy Oral	Caution: hemorrhagic events, atrial fibrillation/flutter, prolongation of PR interval, hyperuricemia, TLS, hepatitis B reactivation possible; anemia, neutropenia, thrombocytopenia; diarrhea; infections; lymphocytosis; hyperuricemia; muscle and bone pain	Monitor patient and provide education on signs/symptoms of serious side effects and when to contact HCP; educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, preventative measures and when to contact HCP; provide education on need for adequate rehydration if diarrhea persists/becomes severe
Nivolumab Immunotherapy (Checkpoint inhibitor) IV	Immune-mediated adverse events (abnormal endocrine function, diarrhea/colitis, elevation in liver enzymes, nephritis, pneumonitis, rash)	Monitor and educate about immune-related events, which can occur any time and should be identified, reported and treated early
Obinutuzumab Monoclonal antibody IV	Infusion-related reactions; hyperuricemia, TLS; neutropenia, thrombocytopenia; hepatitis B reactivation; infection; hepatic enzyme elevations; hyperuricemia	Premedication recommended for all infusions; initiate institutional protocol for management of infusion-related reactions; initiate appropriate interventions for TLS; monitor lab values; educate patients on side effects including increased infection risk, signs/symptoms of infection, signs/symptoms of bleeding, preventative measures and when to contact HCP
Oxaliplatin Alkylating agent IV	Vesicant; peripheral sensory neuropathy (cumulative, dose-related, reversible); nausea/vomiting; fever; leukopenia, thrombocytopenia; risk of secondary malignancies	Initiate recommended procedures to prevent drug extravasation; educate patient on signs/symptoms of drug extravasation; administer antiemetics; administer acetaminophen for infusion-related fever; educate patients on side effects including increased infection and bleeding risk, signs/symptoms of bleeding/infection, preventative measures and when to contact HCP
Pembrolizumab Immunotherapy (Checkpoint inhibitor) IV	Efficacy affected by systemic corticosteroids or immunosuppressants; infusion-related reactions; immune-mediated adverse events (abnormal endocrine function, diarrhea/colitis, elevation in liver enzymes, nephritis, pneumonitis, rash)	Premedication recommended for all infusions; initiate recommended procedures to prevent drug extravasation; initiate institutional protocol for management of infusion-related reactions; monitor and educate about immune-related events, which can occur any time and should be identified, reported and treated early;

CAR T, chimeric antigen receptor T cells; HCP, healthcare professional; IV, intravenous; TLS, tumor lysis syndrome
Sources: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#i-content; https://voice.ons.org/news-and-views/nursing-considerations-for-adverse-events-from-car-t-cell-therapy; https://www.cancernetwork.com/view/managing-car-t-cell-therapy-patients-hematologic-malignancies

Tumor lysis syndrome (TLS)

Tumor lysis syndrome (TLS) is a potentially serious complication of cancer treatment and is characterized by metabolic and electrolyte abnormalities caused by the disintegration of malignant cells by therapeutic agents and the resulting rapid release of intracellular contents in peripheral blood. If untreated, progression of TLS may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control and death (NCCN 2020b).

Symptoms of TLS are generally nonspecific and can include:

- Nausea with or without vomiting
- Lack of appetite and fatigue
- Dark urine, reduced urine output or flank pain
- Numbness, seizures or hallucinations
- Muscle cramps and spasms
- Heart palpitations

Clinical and laboratory manifestations of TLS:

- Hyperuricemia (uric acid > 8 mg/dL)
- Hyperphosphatemia (phosphorus > 4.5 mg/dL)
- Hyperkalemia (potassium > 6 mmol/L)
- Hypocalcemia (corrected calcium < 7 mg/dL, ionized Ca < 1.1)
- Marked elevation of lactate dehydrogenase (LDH)
- Acute kidney injury
- Cardiac arrhythmias
- Seizure/neuromuscular irritability (Emadi 2018)

Prevention measures for TLS:
Prevention of TLS in those patients at risk is the best management. Standard prophylaxis includes hydration with diuresis and administration of allopurinol or rasburicase (NCCN 2019)
Treatment measures for TLS:

- IV fluids
- Allopurinol or rasburicase
- Management of hyperuricemia
- Frequent monitoring of electrolytes and aggressive correction

Cytokine release syndrome

Cytokine release syndrome (CRS) can occur after treatment with some types of immunotherapy, such as monoclonal antibodies and CAR T-cells. It is caused by a large, rapid release of cytokines into the bloodstream from immune cells affected by immunotherapy.

Clinical manifestations of CRS:

- Fever, chills, fatigue, anorexia, myalgia, arthralgia
- Headache, altered mental status, delirium, aphasia, hallucinations, tremor, abnormal gait, seizures
- Skin rash
- Nausea, vomiting, diarrhea
- Tachypnea, hypoxemia, acute respiratory distress syndrome
- Tachycardia, hypotension, widened pulse pressure, cardiomyopathy
- Azotemia, elevated creatinine
- Transaminitis, hyperbilirubinemia (Emadi 2018)

Management of CRS includes:

- Grade 1 (non-life-threatening symptoms) and Grade 2 (symptoms require moderate interventions) in the absence of comorbidities: Supportive care including treatment of febrile neutropenia; monitor fluid balance; administration of antipyretic medications; close monitoring of cardiac, renal and hepatic function
- Grade 2 (with comorbidities and in older patients), Grade 3 (symptoms require aggressive treatment), Grade 4 (presence of life-threatening symptoms): Aggressive supportive care plus tocilizumab with or without corticosteroids (Emadi 2018)

Neurotoxicity

Neurotoxicity is an important and common complication of CAR-T cell therapies and is closely associated with CRS. Acute neurologic signs and/or symptoms occur in a significant proportion of patients treated for B-cell malignancies. Clinical manifestations include headache, confusion, delirium, language disturbance, seizures and rarely, acute cerebral edema. Corticosteroids, interleukin-6-targeted therapies, and supportive care are frequently used to manage patients with neurotoxicity, but high-quality evidence of their efficacy is lacking (Gust 2018).

Common problems experienced before, during and immediately following treatment

Fatigue

Fatigue is experienced by the majority of cancer patients and can be a major cause of reduced physical functioning and lowered quality of life (Snowden 2011). Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning (NCCN 2020c). In comparison to fatigue in healthy individuals, cancer-related fatigue is less likely to be relieved by rest, is more distressing and differs in daily evolution profiles (Glaus 1996). It can be unpredictable, intense and manifest as an overwhelming sense of tiredness or energy depletion. Fatigue may be cumulative, with an increase in the presence of other physical symptoms, mood disturbances and changes in usual activity (Johnston 2001). A review of theoretical and research literature on cancer-related fatigue identifies three core activities to reduce the effect of fatigue: effective management of associated symptoms, enhancement of activity balanced with rest and management of emotional stress (Ream 1999).

Table 3. Causes and Management of Common Problems experienced by Patients with Lymphoma Before, During and Immediately Following Treatment[a]

Problem	Cause	Management by HCP
Alopecia (hair loss)	Alkylating, anthracycline agents and radiation therapy; severity dependent on type and dose of agent, individual sensitivity	Provide education on cause/duration of alopecia; provide psychosocial support; counsel regarding wig/head protection
"B" or inflammatory symptoms (fever, drenching night sweats, loss of >10% of body weight)	May be related to cytokine production	Administration of antipyretics; adequate hydration; symptoms often subside with initiation of treatment
Bleeding	Chemotherapy-induced thrombocytopenia; risk increases as platelet count decreases; risk of spontaneous bleeding with platelet count <20,000/mm^3	Obtain patient history of bleeding; initiate bleeding precautions; monitor CBC, differential and platelet count; examination of mucous membranes, sclerae, skin; neurologic assessment for symptoms of intracranial bleeding
Bone health	Steroid-containing systemic therapy can increase risk of fractures and treatment-induced bone loss	Evaluation of vitamin D levels, post-treatment bone mineral density evaluation; ensure adequate calcium intake; hormone replacement therapy; bisphosphonates or denosumab administration
Diarrhea	May be chemotherapy-related, and/or radiation therapy to abdominal area	Evaluate electrolyte levels if severe; administer antidiarrheal medication in the absence of GI infection; maintain/increase fluid intake; provide electrolyte replacement; obtain stool specimen for evaluation of enteric pathogens; oral nutritional supplements if indicated
Fatigue	Multifactorial causes including treatable causes (anemia), psychological (depression, decreased coping ability) and disease- and treatment-related causes	Provide information about causes; use fatigue assessment tool/scale for systematic/comprehensive collection of data on patient's experience of fatigue; administer erythropoiesis stimulating agents or red blood cell transfusions to correct anemia; consider antidepressants for depression/anxiety; work with patient to identify energy conservation practices; encourage optimal level of activity
Infection	Chemotherapy-induced neutropenia, immunosuppression; risk varies according to type & dose of chemotherapy	Preventative measures (handwashing, avoidance of persons with infection, oral hygiene and skin care, surveillance screening cultures) paramount to reducing risk & severity; regular assessment and early recognition of signs & symptoms; prompt initiation of treatment (broad-spectrum antibiotic coverage)
Loss of appetite/weight loss	Commonly experienced, may be unexplained; taste changes related to chemotherapy	Stimulate food intake, increase body weight, decrease energy expenditure, enhance nutrient absorption; referral to dietician; oral nutritional supplements; cannabis derivatives
Nausea/vomiting	Severity varies depending on emetogenic potential of antineoplastic agents and individual patient characteristics; onset may be immediate or delayed	May be self-limiting; offer antiemetic; avoid noxious stimuli; may require IV fluids or nutritional support if severe
Oral ulcerations (mucositis/stomatitis)	Damage to the mucosal epithelium caused primarily by chemotherapy; can lead to difficulty swallowing, weight loss, anorexia, dehydration, infection	Oral care 5-6 times/day; administration of local/ systemic analgesics; dietary modifications (moist/ soft foods; avoidance of acidic, spicy, salty foods)
Peripheral neuropathy	Associated with vinblastine, vincristine and brentuximab vedotin	Currently no effective medications to relieve neuropathic symptoms; can impact QoL due to physical, social and psychological effects of unrelieved pain

Table 3. Causes and Management of Common Problems experienced by Patients with Lymphoma Before, During and Immediately Following Treatment[a]

Problem	Cause	Management by HCP
Progressive multifocal leukoencephalopathy	Rare but potentially fatal CNS infection caused by reactivation of latent JC polyomavirus; occurs with severe immunosuppression; can occur in NHL with rituximab + chemotherapy or brentuximab vedotin	No effective treatment, risk patients should be closely monitored for the development of neurologic symptoms (confusion, motor weakness or poor motor coordination, loss of balance, visual changes and/or speech changes)
Pruritus	Common in HL where itching/burning symptoms are localized, more generalized symptoms in NHL; may occur as a result of lymphoma or treatment	Often subsides with initiation of treatment; topical preparations (emollient creams/lotions) applied 2-3 times/day; topical corticosteroids; systemic administration of anti-histamines, serotonin-inhibitors, antibiotics (if infection present); cold compresses; minimize/eliminate provocative factors
Pulmonary dysfunction	Bleomycin-containing chemotherapy regimens. Risk factors: older age, cumulative dose, pulmonary irradiation, history of lung disease	Monitor for signs & symptoms of respiratory distress
Hepatitis B virus reactivation	Can occur following cancer treatment, especially with the use of immunosuppressive agents	Testing for patients who will receive anti-CD20 monoclonal antibodies (e.g., rituximab); antiviral prophylaxis or pre-emptive therapy

[a] Problems presented in this table can be related to lymphoma, the side effects of treatment and/or the side effects/complications of hematopoietic cell transplant (HCT)
CNS, central nervous system; GI, gastrointestinal; HL, Hodgkin lymphoma; IV, intravenous; NHL, non-Hodgkin lymphoma; QoL, quality of life
Sources: Derbyshire 2013; EONS 2012; Johnson 2016; NCCN 2020b; NCCN 2020c; Tariman 2008; www.lymphomas.org.uk

Side effects of radiation therapy

The type and severity of side effects related to radiation therapy generally depend on the area of the body being treated and the dose delivered (**Table 4**) (Poirier 2013). Major advances in radiation techniques have made it more precise thus reducing the severity and duration of side effects. Reactions often start during the second or third week of treatment and may last for several weeks after the final treatment.

Table 4. Side Effects of Radiation Therapy to Specific Fields

Radiation field	Potential side effects
Skin	Redness, irritation, swelling, blistering, discoloration Dryness, itchiness, peeling
Head & neck	Oral mucositis, xerostomia Swallowing difficulties, nutritional deficiencies
Mediastinal area	Esophagitis Nausea, Loss of appetite Painful swallowing Pneumonitis
Pelvis Abdominal area	Nausea, vomiting Radiation cystitis Diarrhea
Any field	Fatigue

Adapted from: Poirier 2007

The management of most of the side effects related to radiation therapy is similar to that for systemic lymphoma treatment as described in **Tables 2** and **3**. Radiation skin reactions or radiation dermatitis occurs in nearly all patients. Most radiation therapy centers have their own protocols for management of irradiated skin areas. Some general recommendations for managing skin problems include:

- Routine skin assessment performed at baseline prior to initiation of treatment and at minimum once per week.
- Continuation of usual personal hygiene practices during treatment. The affected area should be cleansed with mild soap or a pH-neutral cleanser and water and patted dry using a soft towel.
- Moisturizing creams and lotions may be used as long as the skin is intact
- The irradiated area should be protected from extreme heat or cold
- Patients should wear loose fitting clothing
- A sunscreen with SPF 30 should be applied (Poirier 2007)

Management of the Patient undergoing Hematopoietic Cell Transplant

Hematopoietic stem cell transplant (HCT) is an intensive treatment option for lymphoma, especially for durable treatment response and a potential for increased survival. those patients with aggressive disease or with relapsed/ recurrent disease. For most patients, HCT provides a HCT requires chemotherapy with or without total body irradiation as part of preconditioning for the transplant and the use of immunosuppressants, which all contribute to an increased risk of infections. There are two types of HCT: allogeneic and autologous transplant. Generally, autologous HCT is a more common treatment option in lymphomas than is allogeneic HCT transplant [see Module 2 and Module 3 for a detailed explanation of treatment recommendations].

In addition to clinical complications of HCT, patients experience distressing physical and psychological symptoms such as severe fatigue, weakness, sleep disturbances, anxiety, lack of appetite, bowel problems and pain (Cohen 2012; Bevans 2008). Patients undergoing HCT reported a steep deterioration in QoL and substantially worsening depression during hospitalization, which were correlated with baseline anxiety and depression (El-Jawahri 2014). Patients may experience disappointment and fear should the transplant fail and express feelings of anger, betrayal, grief, depression and hopelessness (Hutt 2018).

Longer-term health-related issues

While allogeneic HCT may cure the underlying lymphoma, there is a strong risk for late complications that can cause functional deficits and negatively affect QoL. Hence, screening and preventive practices for long-term survivors of HCT are strongly recommended (see Majhail 2012). Plans of care and educational efforts should be directed at individual patient needs to help them and their caregivers better cope and manage the late effects of HCT (Valenta 2017).

Support and Facilitation of Shared Decision-making

Components

Shared decision-making is a process that involves both the patient and the clinician discussing management options and agreeing on management decisions in partnership (Thistlethwaite 2006) based on the best available evidence (Härter 2004). Shared decision-making centers around patient preferences and options. According to Fraenkel (2007), shared decision-making must include:

- An adequate level of patient knowledge about the condition in question
- Explicit encouragement of patient participation by the clinician
- Appreciation of the patient's responsibilities and rights in active decision-making
- Awareness of the options and the implications of the choice made
- Sufficient time to engage in collective deliberation

Patient/healthcare professional factors in shared decision-making

Although scant evidence exists, presumably shared decision-making leads to better health outcomes because patients offer more useful information enabling providers to identify more robust clinical options. Patients may be more motivated to follow recommendations that they were involved in formulating (Clark 2009). Patients vary in their preferred level of participation in cancer treatment decision-making, which is influenced by patient characteristics such as age, sex, race/ethnicity, cancer type and individual values and beliefs (Kane 2014). Caregivers and partners can support patients to manage information they receive and the engagement of caregivers in decision-making may encourage more frequent discussion about treatment options.

There are reported differences in the willingness of healthcare professionals to participate in shared decision-making with their patients. One small study conducted in Germany found great variation in the attitudes and experiences of oncology healthcare professionals towards shared decision-making (Frerichs 2016). The variations in attitudes were particularly present in terms of their attitude towards the degree of patient involvement in decision-making and their assumptions about the situations in which shared decision-making should take place. In another study, physicians felt that shared decision-making was likely to result in patients making the wrong decision; in particular, patients wanted treatments with the best chance of survival (Shepherd 2011). Cancer care often occurs over an extended period of time and entails multiple treatment types and often various specialists. Patients may not be aware of the influence of one treatment over another or of the need to revisit decisions along the cancer care continuum. In light of these and other confounding variables present in cancer care, a review of the literature on shared decision-making concluded that while patients seem to be supportive of shared decision-making, clinicians are relatively less enthusiastic and less likely to adopt it as a consultation strategy (Clark 2009).

Strategies for implementation of shared decision-making

A patient-centered approach in shared decision-making in cancer care is necessary due to the complexity of cancer care and the serious implications of patient treatment choices for their health outcomes and quality of life. Further, evidence supporting many decisions in cancer care is limited or incomplete (Kane 2014). Nurses are key patient advisors and counselors in practice settings where shared decision-making is an increasing expectation (Clark 2009) and they play an increasingly larger role in the ongoing care and management of long-term conditions, including cancer care. In this role they are well positioned to engage patients in shared decision-making and assist them to make clinical choices.

The process of decision-making should be carefully considered. Patients and their caregivers require information on the decision being made and their understanding of that information needs to be assessed throughout the process. The steps of shared decision-making include:

- Recognize that a decision can or must be made and inviting the patient (and caregiver) to participate in the process
- Identify the possible courses of action and options
- Review and list the benefits, risk and other characteristics of each treatment option by providing balanced information based on the best medical evidence
- Compare options and identify the "best" option based on the patient's goals and concerns
- Facilitate deliberation and decision-making by letting patients know they have time for considering treatment choices
- Authorization of the final choice
- Implementation of the choice (Kane 2014; Wexler 2012; Whitney 2008).

Cancer Survivorship

Cancer survivorship starts at the time of initial diagnosis and encompasses the experience of living with, during and after a cancer diagnosis. While there have been tremendous advances in multimodal therapy for lymphomas, survivors remain at risk for complications that may persist or develop years after therapy is completed and the achievement of long-term quality of life (QoL) in these patients is an ongoing challenge. A survey of over 900 lymphoma survivors revealed that while the population experienced excellent disease outcomes, they reported a substantial burden resulting from late and long-term effects of treatment, most especially peripheral neuropathy and fatigue (Frick 2018).

Because of the long-term sequela of lymphoma treatment, it is important that patients understand and comply with the need for regular medical checkups and tests. To be an active participant in follow-up care, patients need to feel comfortable to express their concerns about their current and future health status. Maintaining a list of questions and/or a personal health journal may aid in remembering points for discussion during follow-up visits. Having a family member or friend accompany the patient to medical appointments is often advantageous as "four ears" are often better than two.

Self-management (making decisions that involve taking control of one's health and well-being) involves taking an active role in managing diet, exercise and emotional well-being. Encouraging and supporting cancer survivors to attain and/or regain their ability to set goals that are meaningful to them can increase their self-confidence, assist them in coping with late effects of lymphoma or its treatment and possibly improve their quality of life.

Health-related quality of life

Health-related quality of life (HRQoL) is commonly defined as a multidimensional assessment of how disease and treatment affect a patient's sense of overall function and well-being (Cella 1995). In a systematic review of HRQoL conducted by Roper et al (2009), physical, psychological, social/functional and spiritual domains of HRQoL may be compromised for months or even years after completion of treatment. In this analysis, fatigue was the most common problem in the physical domain of HRQoL and several factors may contribute to this result. Total fatigue, for example, was significantly higher among survivors 60 years or older compared to younger HL survivors and those with fewer years of education reported greater fatigue than those with more years of education (Roper 2009). Men experience higher levels of fatigue than women (Norum 1996) and energy levels return later in patients diagnosed with more advanced disease and who receive combination therapy than those with early stage disease and receive monotherapy (Fobair 1986).

In a study of patients with NHL, those individuals who performed 150 minutes or more of moderate to vigorous exercise per week reported better health-related QoL than those who were sedentary (Bellizzi 2009). These authors also note that at least some physical activity, especially in patients who are at risk for poor QoL as a result of treatment, provides significant benefit in health-related QoL (Bellizzi 2009).

Longer-term effects of curative treatment on HRQoL may be especially problematic for younger survivors of

lymphoma due to the longer-term effects of radiation and chemotherapy, especially the use of alkylating agents, that increase the risk of secondary cancers and cardiac disease (Roper 2009).

This analysis also identified other disturbances in HRQoL including a decreased interest in sex and loss of sexual satisfaction, cognitive impairments, depression and anxiety during treatment and for many years after treatment completion (Roper 2009).

Cognition

Cancer survivors often refer to "chemo brain" to describe difficulty thinking clearly before, during and after cancer treatment. Healthcare professionals use terms such as cancer treatment-related cognitive impairment, cancer-related cognitive change or post-chemotherapy cognitive impairment to refer to this condition. Changes in cognition may also be due to hormone therapy, radiation and surgery.

The effects of chemo brain vary in severity and may be experienced as problems concentrating, multitasking or understanding or remembering. For most patients, mental changes are short term. However, others can have long-term or delayed mental changes.

Exercise, meditation, using a detailed daily planner, writing reminder notes and exercising the brain by doing word puzzles or other mentally stimulating activities may help to sharpen mental abilities and manage chemo brain.

Emotional changes

There is a broad range of emotions, both negative and positive, experienced by cancer survivors. Some of these are relief, a sense of gratitude to be alive, fear of recurrence, anger, guilt, depression, anxiety and isolation (ASCO 2017). Patients should be encouraged to acknowledge these feelings and to talk with a nurse, social worker or another member of the healthcare team about them. The inability to cope with these emotions could begin to negatively affect daily activities or relationships.

Sexuality

Changes in sexual function or sex drive caused by cancer and cancer treatment can occur. Physical changes not related to sexual function may affect feelings about body image or function. Open and honest communication about these feelings with a partner or with a counselor may help the patient recognize and adapt to changes in sexuality and intimacy.

Strategies for coping with changes in HRQoL

- Talk with the healthcare team
- Recognize emotions
- Maintain healthy habits such as eating nutritious meals, exercising regularly, getting enough sleep
- Manage and reduce stress
- Re-evaluate old patterns and priorities
- Reach out for spiritual support
- Keep a journal or blog
- Explore new ways to support emotional well-being

Fertility and family planning

Certain chemotherapy combinations (e.g., BEACOPP for HL) may cause immediate and permanent infertility in both men and women (NCCN 2020a). Chemotherapy with alkylating agents is also associated with infertility although the fertility risks of any chemotherapy agent should be considered (Corbitt 2018). A discussion of the known and possible effects of treatment on fertility should be conducted at the time of diagnosis.

Topics to be considered for discussion with *female* patients include:

- Providing education on options, refer to a fertility specialist early. Time for decision-making may be difficult as treatment for lymphoma may be started quickly
- Ideally, egg harvest should take place before initiation of treatment. The cost of egg and/or embryo preservation is often prohibitive, referral to a nonprofit assistance program might be appropriate
- The necessity to make decisions on future family planning may adversely impact QoL; patient may need to grieve the loss of natural family planning option (Corbitt 2018)

Topics to be considered for discussion with *male* patients include:

- Discuss options for cryopreservation of sperm; consider sperm donor if cryopreservation is not possible
- Consult patient/family on financial implications of sperm bank fees
- Stress of diagnosis and speedy decisions on fertility issues may cause undue burden and unsuccessful attempts at sperm collection
- Consider fertility risks of any chemotherapy agent to be used (Corbitt 2018)

Follow-up Care

Post treatment follow-up

Schedules for follow-up after completion of treatment for aggressive types of lymphoma should be individualized and based on patient age, stage of disease and initial treatment modality (NCCN 2020a). Follow-up with an oncologist is recommended and should be coordinated with the primary care physician, especially during the first 5 years after treatment to detect recurrence. Physical exams are generally carried out more frequently in the immediate period after treatment concludes and then spaced farther apart in later years. For example, history, physical examination and laboratory analysis including full blood cell count ESR testing and blood chemistry should be performed every 3 months for the first half year, every 6 months until the fourth year and once a year thereafter (Eichenauer 2018).

Thyroid stimulating hormone (TSH) testing should be done at least once a year if radiation therapy was administered to the neck area.

Minimal imaging tests (CT scans) of the neck, chest, abdomen and pelvis at 6, 12 and 24 months after completing treatment are often performed. There is no definitive evidence that routine PET imaging in patients in complete remission is advantageous (NCCN 2020a; Eichenauer 2018; Tilly 2015).

Longer-term follow-up

Although there is not a standard care schedule to be followed after treatment with curative intent, monitoring the patient for relapse during the first 5 years after treatment is important. Continued longer-term follow-up is also necessary to detect late effects of therapy such as secondary cancers, cardiovascular disease, hypothyroidism and fertility issues. The incidence of these late effects increases with longer follow-up, although risk may be less with current treatment regimens as compared to those used in the past.

Secondary malignancies

Cancer screening should be conducted regularly due to the persistently increased risk for the development of hematological and solid second malignancies after treatment. Longer-term follow-up is important as secondary malignancies, especially solid tumors, can develop more than 10 years after the completion of treatment (NCCN 2020a). There appears to be an association between the type of lymphoma treatment and the risk of secondary cancers. Retrospective data indicate that both radiation therapy dose and field size, as well as intensity of chemotherapy, particularly alkylating agents and etoposide, correlate with an increased incidence of secondary malignancies (Swerdlow 2011). A family history of colorectal, lung or breast cancer was shown to increase the risk of second cancers in comparison to survivors without a family history (Sud 2017).

Both hematologic neoplasms and solid tumors form the largest cause of mortality in long-term survivors of HL and these survivors are at 13 times higher risk of developing a second primary NHL (Shanbhag 2018). The risk of female breast cancer secondary to radiotherapy is particularly high in those who received radiation when younger than 30 years of age, and the incidence remains for decades after completion of radiotherapy (Shanbhag 2018).

The NCCN (NCCN 2020a) recommends performing routine surveillance tests for cervical, colorectal, endometrial, lung and prostate cancer. Annual dermatologic examination may be especially important in the HL population due to the known increase in skin cancer risk after radiation (Ng 2014).

Female patients who were ≤40 years at the time of chest or axillary irradiation should have a mammography once a year starting 8 to 10 years after radiation therapy. Those who were ≤30 years should have a breast MRI in addition to mammography (Eichenauer 2018). These patients should be encouraged to perform monthly breast self-examination.

Cardiovascular disease

Cardiovascular disease following cancer treatment is the leading non-cancer-related cause of death in Hodgkin lymphoma survivors (Gupta 2015). The administration of both mediastinal irradiation and anthracycline agents increases risk for developing cardiac disease, which may be asymptomatic. In symptomatic patients, clinical manifestations of cardiovascular disease, especially disease related to anthracycline administration, are arrhythmias or cardiomyopathy, which can lead to congestive heart failure. Cardiotoxicity secondary to radiation therapy can occur more than 5 to 10 years after completion of treatment, although symptoms may be evident at any time (NCCCN 2020a).

Hypercholesterolemia and hypertension are factors contributing to an increased risk of cardiovascular disease. Recommendations are, therefore, to obtain a lipids panel test to measure total cholesterol level, triglyceride level and HDL and LDL cholesterol levels twice per year and to regularly monitor blood

pressure and aggressively manage any cardiovascular risk factors. NCCN (2020a) recommends a stress test/ECHO and/or a carotid ultrasound at 10-year intervals after treatment is completed. Aggressive measures to reduce cardiovascular risk factors including the encouragement of a balanced diet, regular physical activity and smoking cessation should be encouraged (Lin 2019).

Pulmonary toxicity

Pulmonary toxicities can arise acutely and subacutely during treatment (bleomycin or radiation-induced pneumonitis) and may lead to chronic respiratory impairment. Irradiation doses to the mediastinal area above 20 Gy dramatically increase the risk of a decline in pulmonary function over time (Armenian 2015). Bleomycin-induced pulmonary toxicity (BPT) is well documented in patients with HL treated with bleomycin-containing chemotherapy regimens. Risk factors include older age, cumulative bleomycin dose, pulmonary irradiation and prior history of lung disease. BPT has an effect on 5-year overall survival, especially in patients aged 40 years or older. The use of growth factors with chemotherapy may increase the incidence of BPT (Andersen 2019).

Hypothyroidism

Abnormal thyroid function is reported in about 50% of long-term survivors who received neck or upper mediastinal irradiation with 90% of patients experiencing hypothyroidism (Ha 2014). Thyroid dysfunction can occur as late as 26 years after treatment. Two factors predict the risk of hypothyroidism: dose of radiation and the percentage of thyroid gland exposed.

Signs and symptoms of hypothyroidism include: Fatigue, weight gain, cold intolerance, weakness, cardiac dysfunction, cognitive difficulties, depression.

Measures to be taken to monitor for hypothyroidism are annual monitoring of thyroid-stimulating hormone and free thyroxine along with a thorough physical exam and review of the patient's state of health.

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Quick Facts

- The decision on whether therapy should be administered during pregnancy is highly individualized and based on the clinical scenario and patients' wishes
- Chemotherapy administration during the first trimester of pregnancy is contraindicated due to adverse effects on the fetus. Chemotherapy during the second trimester is likely safe and deferring treatment until the postpartum period is safest for mother and child, when the situation allows
- While the number of cases of lymphoma in older people is expected to steadily rise, the presence of comorbidities, malnutrition and/or impairments in functional status affect prognosis, treatment considerations as well as the achievement of complete remission
- In light of the cardiotoxicity associated with doxorubicin, this agent should be substituted by drugs such as gemcitabine, etoposide or a liposomal formulation of doxorubicin in vulnerable elderly patients with comorbidities
- Newer three-drug antiretroviral therapy regimens have increased the overall survival (OS) for patients with HIV-associated lymphoma from < 20% to > 80%
- The clinical course of HIV-associated lymphoma is more aggressive and the disease is both more extensive and less responsive to chemotherapy than in other lymphoma patients; immunodeficiency and cytopenia are exacerbated by the administration of chemotherapy and treatment increases the risk of opportunistic infections
- Immunosuppressive agents used after solid organ or stem cell transplant diminish the quantity and quality of T-cells making them unable to produce cytokines essential for immune destruction. This altering of T-cell function increases the risk of developing post-transplant lymphoproliferative disorders (PTLD)
- Treatment of PTLD, which may involve reducing doses of immunosuppressive agents and administering chemoimmunotherapy, should be initiated as soon as possible due to the risk of rapid tumor growth and multi-organ failure

Module V: Management of Lymphomas in Special Clinical Situations

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    b. Clinical Presentation of Lymphoma in Pregnancy
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            1. Diffuse large B-cell lymphoma
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C. Lymphoma in Patients with Human Immunodeficiency Viruses (HIV)
    a. Considerations
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D. Post-transplant Lymphoproliferative Disorders (PTLD)
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    c. Treatment Approaches in PTLD

References

Management of Lymphoma during Pregnancy

Considerations

Cancer diagnosed during pregnancy poses challenges to the medical team - and to the patient. Hematologic malignancies are the second most common type of cancer diagnosed during pregnancy after breast cancer (Moshe 2017; Van Calsteren 2010). Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) represent roughly 6% and 5% of cancer diagnosed during pregnancy, respectively (Amant 2015). HL is far more common than NHL during pregnancy (Bachanova 2013).

The dilemma in treating lymphoma during pregnancy is achieving a balance between administering effective therapy to the mother while limiting potential toxicity to the unborn fetus (Pinnix 2017).

For the pregnant patient and family, a diagnosis of lymphoma raises special emotional and ethical dilemmas (Moshe 2017). Short- or longer-term effects of treatment may have an effect on fetal development and future fertility. Hence, management of the pregnant woman with lymphoma should be conducted under the guidance of a multi-disciplinary team that includes a maternal fetal medicine specialist as well as healthcare professionals trained in providing psychosocial support.

Clinical Presentation of Lymphoma in Pregnancy

Pregnant women with aggressive lymphomas may present with an advanced stage disease due to delay in diagnosis, as there are similarities in clinical symptoms of lymphoma and pregnancy. Additionally, pregnancy itself may obscure symptoms and clinical findings of lymphoma.

Diagnosis and Staging of Lymphoma in Pregnancy

As with other patients, pathologic examination of lymph node biopsy specimen(s) should be performed to make the diagnosis of HL or NHL (Pinnix 2017). Both core and excisional lymph node biopsy as well as bone marrow biopsy are feasible and considered safe during all gestational stages (Weisz 2004; Andtbacka 2013). Laboratory values for erythrocyte sedimentation rate (ESR) or lactate dehydrogenase (LDH) may be elevated due to gestation and not necessarily disease-related factors. Results of some serum studies should be interpreted with caution because an elevation of markers can occur due to gestation and not necessarily disease-related factors.

In terms of imaging techniques, the guiding principle is to restrict radiologic staging to the minimum necessary to identify disease that seriously threatens the immediate well-being of mother or child (Bachanova 2016). Computed tomography (CT) and positron emission tomography (PET) should be avoided, especially during early stages of gestation, or reductions to the dose to the abdominopelvic area should be made and abdominal shielding used owing to radiation exposure of the fetus (Austin 2011). The highest risks to the fetus from radiation occurs during the first trimester of pregnancy and with radiation exposures of over 100 mGy (McCollough 2007). Abdominal ultrasonography may be useful in identifying the extent and size of retroperitoneal nodal involvement. Magnetic resonance imaging (MRI) without use of gadolinium can be used if further detailed imaging is required (Bachanova 2016). Any diagnostic study requiring imaging should be administered at doses of less than 5 cGy to the fetus and each case should be considered individually in consideration of the radiation exposure to the fetus and associated predicted risks (Pinnix 2017).

Treatment Considerations in Pregnancy

The primary considerations in making treatment decisions in this population are:

- gestational age of the fetus at the time of diagnosis
- stage and aggressiveness of the disease
- presence of life-threatening symptoms (Pinnix 2017).

With adequate and appropriate chemotherapy, survival rates of pregnant patients with NHL are similar to those of non-pregnant controls (Pinnix 2017).

The use of chemotherapy during the first trimester of pregnancy is considered dangerous to the fetus; systemic therapy given after the first trimester (if deferring treatment would not compromise maternal outcome) is likely safe and results in acceptable maternal and fetal outcomes (Pinnix 2016). In low-risk patients, such as those with HL stage I, II and even III, and low-grade NHL, therapy can be deferred until the end of the first trimester or even further into the later stages of pregnancy if the patient is closely monitored. Deferring treatment until after the baby is delivered is often possible for those women diagnosed with lymphoma during the 3rd trimester.

The decision on whether therapy should be administered during pregnancy is highly individualized and based on the clinical scenario and patients' wishes (Kritharis 2016). The goals in treating lymphoma during pregnancy focus on maternal outcomes, fetal outcomes and obstetric outcomes.

Maternal outcomes: overall survival and progression-free survival

Fetal outcomes: fetal demise, admission to a neonatal intensive care unit, malformations and low gestational age

Obstetric outcomes: preterm delivery (before 37 weeks gestation), spontaneous preterm delivery, postpartum hemorrhage, preeclampsia, gestational diabetes, endometritis and route of delivery (Kritharis 2016).

There are other issues to be considered in treating the pregnant woman with lymphoma. Firstly, there is a lack of adequate pharmacokinetic data on the effects of chemotherapy in pregnancy. The physiological changes during pregnancy may affect the distribution, metabolism and excretion of administered chemotherapy agents. Lastly, because the biodistribution of chemotherapeutic agents may be affected by pregnancy, it may be necessary to administer higher chemotherapeutic dosages to achieve optimal blood levels (Moshe 2017).

There is no strong rationale for administering radiation as monotherapy during pregnancy and, due to uncertainty regarding the long term effects of radiation on the fetus, there is general agreement that radiation therapy should be avoided during pregnancy (Moshe 2017; Pinnix 2016).

Treatment Approaches in Pregnant Patients with Hodgkin Lymphoma (HL)

Newly diagnosed

HL is usually initially diagnosed at the same disease stage as in non-pregnant counterparts and outcomes in women diagnosed in pregnancy do not appear to be worse than those in age-matched women (Pinnix 2017).

Although ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) is standard treatment for HL, due to the risk of teratogenicity during the first trimester, chemotherapy and especially combination chemotherapy should be avoided (Moshe 2017). In the first pregnancy trimester, the most recommended strategy is to postpone combination chemotherapy with ABVD to the second trimester of pregnancy. Strategies to safely manage these women until the second trimester include:

- administration of steroids or
- single-agent vinblastine (Odelia 2017; Bachanova 2013).

Women with advanced HL diagnosed at an early pregnancy stage whose condition requires immediate intervention with intensive therapy should start chemotherapy immediately with pregnancy termination strongly recommended. Women with early-stage HL diagnosed in the first trimester can be closely followed for signs of disease progression and start chemotherapy in the second trimester.

Women with HL diagnosed in the second or third trimester can be treated with ABVD, which is considered relatively safe in this population (Azim 2010). Treatment with escBEACOPP (escalated bleomycin, etoposide, doxorubicin hydrochloride [Adriamycin], cyclophosphamide, vincristine [Oncovin], procarbazine and prednisone) is considered too toxic to the fetus and, therefore, not recommended during pregnancy.

Given the efficacy of systemic therapy, radiation therapy, especially monotherapy with radiation, is not recommended during pregnancy. In cases of adverse disease effects, such as superior vena cava syndrome or spinal cord compression, radiation can be considered with extreme caution and using shielding to reduce fetal exposure (Pinnix 2017).

Recurrence during pregnancy

In women treated for lymphoma while not pregnant, there appears to be no increased risk of pregnancy-associated relapse after completion of treatment (Weibull 2016) and there are very few case reports of women relapsing during pregnancy.

The standard treatment in non-pregnant patients with relapsed disease is platinum-based chemotherapy followed by high-dose therapy with autologous stem cell transplantation. There is, however, limited data on the safety of these protocols in pregnancy. For this reason, an option for women previously treated for lymphoma and now experiencing relapse during pregnancy is retreatment with ABVD (Moshe 2017). Because of the generally higher risk of relapsing within the first 2 to 3 years after diagnosis, it is suggested that women delay pregnancy until after the first 2 years of therapy completion if possible (Pinnix 2017).

Treatment Approaches for Pregnant Patients with Non-Hodgkin Lymphoma (NHL)

Since non-Hodgkin lymphomas, such as diffuse large B-cell lymphoma (DLBCL), usually occur later in life, they rarely occur during pregnancy, affecting 0.2 to 0.7 in 100,000 pregnancies (NTP 2013). Chemotherapy during pregnancy is often necessary in women with DLBCL diagnosed early, at an advanced stage, or as an aggressive subtype (Hersey 2020).

In pregnant women with NHL, combination chemotherapy using the most common regimens that are standard for the particular lymphoma subtype and extent of disease are often used (Evens 2013). These include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone) administered during second and third trimesters, which are associated with minimal maternal complications or fetal detriment (Evens 2013). In addition, patients with low-risk clinical scenarios (e.g., indolent NHL, low tumor burden, and/or late gestational diagnosis) can safely defer therapy to postpartum (Evens 2013).

Future Perspectives

The normal physiological changes that occur during pregnancy may influence pharmacokinetics and pharmacodynamics of chemotherapeutic agents. Hence, there is a need for pharmacokinetic studies in pregnant women receiving chemotherapy. Genome sequencing of cell-free fetal DNA present in maternal plasma may be helpful for diagnosis of cancer in asymptomatic pregnant patients. This technology could also have implications for early detection of tumors in women contemplating pregnancy post therapy.

Older Patients with Lymphoma

Considerations

The number of elderly patients with hematological malignancies is expected to rise continuously since these disease entities are typical diseases of the elderly, with a median age at initial diagnosis of > 70 years for most of the common lymphoma subtypes, such as diffuse large B-cell lymphoma (DLBCL). On a positive note, the number of treatment options has increased dramatically over the past years, ranging from best supportive care to hematopoietic stem cell transplantation (Buske 2018).

As might be expected, the presence of comorbidities, malnutrition and/or impairments in functional status affect prognosis, treatment considerations as well as the achievement of complete remission (CR).

Treatment should aim to be curative for all disease stages with attention given to serious treatment-related toxicities including treatment-related mortality, especially for frail patients. At present, however, evidence-based treatment algorithms and recommendations for elderly patients with lymphoma are rare, in part due to the lack of inclusion of elderly patients in clinical trials. Hence, treatment in an elderly patient with lymphoma should be based on individual risk and prognosis, with personalized treatment algorithms based on the integration of age-adjusted models including age-adjusted life expectancy and the evaluation of patient status by geriatric assessment (Wildiers 2013).

Patient Assessment

Assessment of fitness

According to the European Society for Medical Oncology (ESMO) consensus on lymphoma in elderly (Buske 2018), the consideration of fitness in the elderly patient should comprise:

- The type of lymphoma, as it defines the potential aim of treatment
- The treatment, as it defines the risk of toxicity
- The patient, as the individual characteristics also contribute to toxicity and life expectancy (Buske 2018).

Furthermore, this consensus statement recommends using a geriatric assessment tool to detect impairments, not identified in routine assessments, and to provide a prediction of severe treatment-related toxicity and overall survival (OS). Examples of geriatric-oriented assessment tools include the G8 questionnaire, a simple screening tool, which includes seven mini nutritional assessment items and age, and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), which is useful in quantifying comorbidity. A precise definition of fitness based on scores of geriatric and/or comorbidity tests remains difficult to achieve due to individual patient characteristics and treatment-related toxicities (**Table 1**). Assessment of past medical history, a thorough clinical examination with specific attention to comorbidities and any pre-existing organ dysfunction should be conducted before treatment is initiated. A multidisciplinary team incorporating an oncologist, relevant specialists and supportive services can best address challenges encountered during the management of elderly patients.

Table 1. ESMO Criteria to Define Fitness of Elderly Patients	
Fit patient	Application of the standard treatment, including more dose-intense approaches, is not associated with an increased risk of treatment-related or treatment-unrelated AEs compared with a young fit patient
Vulnerable patient	A high risk for treatment-related AEs or treatment-unrelated AEs when receiving standard treatment. Vulnerable patients present a continuum, ranging from those who are just at the border of not being able to tolerate standard treatment to those who are close to being considered as terminally ill
Terminally ill patient	Has a short life expectancy (about 3 months, due to the lymphoma or comorbidities) and will therefore not benefit from any anti-lymphoma treatment, but only from best supportive care

AE, adverse event; ESMO, European Society for Medical Oncology
Source: Buske 2018

Assessment of frailty

An assessment of frailty is beneficial in predicting outcome. Any method or instrument used to assess frailty should measure several domains of frailty, including comorbidity, psychological health, current quality of life, medication burden, physical health, cognitive function and social support (Böll 2019).

Assessment of quality of life

In addition to decisions regarding treatment efficacy versus toxicity, the balance between quantity and quality of life should be considered in elderly patients. Several tools have been tested and are in wide use for this purpose including the MOS-SF36, the EORTC QLQ-C30 (validated in multiple languages) and the QLQ-ELD14 (developed for use in elderly patients).

Older Patients with Hodgkin Lymphoma (HL)

Clinical outcomes have been acceptable for patients 60 to 70 years of age with early-stage HL, but poor for patients with advanced-stage disease (Bachanova 2016). Outcomes in patients older than 70 years are particularly poor, irrespective of disease stage. This is in part due to comorbidities, which may preclude the use of optimal dose treatments and/or chemotherapy agents with proven efficacy such as bleomycin or anthracyclines.

Choice of treatment modality and intensity are based on initial staging, usually with the use of PET-CT and classification into risk groups (Eichenauer 2018).

Treatment approaches in patients with Hodgkin lymphoma

About one-third of all patients with first diagnosis of HL is above the age of 60 years (Björkholm 2018). Survival rates in older patients, those age ≥ 60 years, have historically been lower than rates in younger patients. Interestingly, the disease biology in older HL patients appears to be different from that in younger patients including increased incidence of mixed cellularity histology and EBV-related disease, and older patients often present with advanced-stage disease.

In early stage favorable disease, (stages I-II), two cycles of ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine) followed by 20 Gy involved-field radiotherapy is internationally accepted as standard of care (Engert 2010; Sasse 2017). Although this regimen is used in older patients, it is associated with high rates of protocol deviation, lower dose intensity and higher severe toxicity resulting in higher treatment-related mortality compared to younger patients (Böll 2013). Retrospective data indicate, however, improved survival with combined treatment as compared to monotherapy (Goyal 2016).

Alternative treatments for this population as recommended by NCCN (2020a) include:

- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), 4 cycles + 30 Gy involved-field radiotherapy
- VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone and bleomycin) ± 30 Gy involved-field radiotherapy

In early-unfavorable-stage HL, four cycles of ABVD chemotherapy followed by localized radiotherapy are widely regarded as standard of care in older patients (Böll 2019).

For advanced HL, 2 cycles of ABVD followed by chemotherapy regimens without bleomycin (AVD), to reduce the risk of bleomycin-induced pulmonary toxicity, is a treatment option in this population (Böll 2019, Eichenauer 2018).

Other treatment regimens recommended by the NCCN (2020a) for stage I-II unfavorable or stage III-IV disease include:

- Brentuximab vedotin followed by AVD
- Brentuximab vedotin + dacarbazine (DTIC)
- CHOP (6 cycles) ± 30 Gy involved-field radiotherapy

- PVAG (prednisone, vinblastine, doxorubicin, gemcitabine) ± 30 Gy involved-field radiotherapy
- VEPEMB (vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin) (6 cycles) ± 30 Gy involved-field radiotherapy

Outcomes in elderly patients who relapse or have refractory disease are uniformly poor. There are no widely agreed upon treatment recommendations and individualized treatment is necessary.

Few treatment options for patients identified as frail are available. Novel non-chemotherapeutic agents, such as brentuximab vedotin, possibly combined with dacarbazine, may provide benefit without increasing the risk of therapy-related toxicity in this population (Böll 2019).

Management of disease- and treatment-related side effects

Pulmonary toxicity, specifically bleomycin-induced lung toxicity (BLT), is a common treatment toxicity following ABVD in elderly patients. The higher risk of severe toxicity is more likely to occur in older HL patients receiving more than two cycles of bleomycin (Böll 2019; Böll 2016).

Older Patients with non-Hodgkin Lymphoma (NHL)

Diagnostic and staging work-up of older patients with diffuse large B-cell lymphoma (DLBCL)

While DLBCL is a curative disease, the treatment of elderly patients with DLBCL is unsatisfactory, with decreasing overall survival rates observed with increasing age due to commonly occurring age-related factors. This physiologic situation makes it difficult to administer dose intense regimens.

The diagnostic workup for elderly patients with DLBCL who are fit for curative treatment should follow standard diagnostic guidelines used for younger patients. Diagnostic investigations include:

- Morphologic and immunophenotypic analyses
- A minimum set of B-cell IHC markers
- Epstein-Barr virus (EBV) confirmation to confirm the possibility of EBV-positive DLBCL
- Routine hematological and biochemical investigations including LDH
- Serologic screening for hepatitis B and C and for HIV status
- Staging using PET-CT imaging; MRI imaging if central nervous system involvement suspected
- Baseline electrocardiogram and left ventricular ejection fraction (LVEF) assessment if anthracycline therapy is a consideration
- Age-appropriate definition of risk score (Buske 2018)

Diagnostic and staging work-up of older patients with peripheral T-cell lymphoma

The median age of patients presenting with peripheral T-cell lymphoma is over 60 years (Buske 2018). While younger patients generally receive intensive treatment and transplant, in elderly fit patients, the aim of treatment is to induce a complete response with induction therapy. For vulnerable patients, the aim of treatment is to control disease using treatment-adapted regimens according to end organ deficit and comorbid conditions. Palliative measures may be the most appropriate to provide a reasonable quality of life for terminally ill older patients.

Diagnostic procedures:

- Excision biopsy to confirm histology
- Staging investigations: CT and PET-CT imaging (most appropriate for fit elderly when curative treatment is being considered)
- Baseline electrocardiogram and left ventricular ejection fraction (LVEF) assessment if anthracycline therapy is a consideration

Treatment approaches for older patients with non-Hodgkin lymphoma

Diffuse large B-cell lymphoma

Fit patients < 80 years with *de novo* disease should receive full-dose R-CHOP as the recommended first-line treatment: the aim of treatment in this population should be curative (Buske 2018). Fit patients > 80 years without comorbidities should receive dose-attenuated R-CHOP. All patients older than 65 should receive prophylactic granulocyte-colony stimulating factor (G-CSF) as the highest incidence of treatment-related mortality occurs within the first two treatment cycles (Böll 2019).

In vulnerable elderly patients with comorbidities, especially cardiac, doxorubicin should be substituted by drugs such as gemcitabine, etoposide or a liposomal formulation of doxorubicin. In cases where a high tumor load is evident, a steroid pre-phase is recommended to optimize performance status and decrease the risk of tumor lysis syndrome (TLS). Radiotherapy to sites of bulky disease may be beneficial.

In relapsed disease and patients who are generally fit and < 70 years old, hematopoietic stem cell transplant should be considered, combined with appropriate salvage treatment using:

- rituximab/dexamethasone/high-dose cytarabine/cisplatin (R-DHAP),
- rituximab/etoposide/methylprednisolone/cytarabine/cisplatin (R-ESHAP),
- rituximab/gemcitabine/dexamethasone/cisplatin (R-GDP) or
- rituximab/ifosfamide/carboplatin/etoposide (R-ICE) (Buske 2018).

For relapsed, transplant ineligible patients, dose attenuated R-DHAP, R-ESHAP, R-ICE, or less intense regimens such as rituximab + gemcitabine + oxaliplatin (R-GemOx) may be appropriate. Single agent chemotherapies such as bendamustine or pixantrone may also be considered.

Peripheral T-cell lymphoma

The CHOP regimen is considered first-line treatment of choice for elderly patients with T-cell lymphomas, although remissions may not be durable (Buske 2018). Support with growth factors may allow higher doses of chemotherapy. Attenuated chemotherapy followed by local radiotherapy may be appropriate treatment for patients who present with early stage disease. Enrollment in clinical trials helps to provide patients with the best options for receiving cutting-edge treatment.

Unlike B-cell lymphomas, peripheral T-cell lymphoma is characterized by a higher incidence of early relapse and refractory disease. Relapsed/refractory disease represents a very poor prognosis in the elderly patient and subsequent treatments are dictated by patient fitness to receive a salvage regimen with gemcitabine or platinum-containing agents. Novel agents such as brentuximab vedotin monotherapy may be an option for patients with CD30+ T-cell lymphoma, enrollment in a clinical trial may offer further alternatives. Transplant is rarely a viable option in this population.

Lymphoma in Patients with Human Immunodeficiency Viruses (HIV)

Considerations

In patients with HIV-induced immune dysregulation, immunologic control of certain oncoviruses such as Kaposi's sarcoma-associated herpesvirus (KSHV), Epstein-Barr virus (EBV), high-risk human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Merkel-cell polyomavirus and virus-infected cells is impaired, which permits the development of cancer (Yarchoan 2018). AIDS-defining lymphoma generally refers to aggressive B-cell NHL arising in patients who have HIV infection.

The presence of HIV also increases the risk of classic HL, which is not AIDS defining. In HIV-associated HL, mixed cellularity is the most common histologic type, the Reed-Sternberg cells are generally EBV-infected and the tumor microenvironment has unique features. HIV-associated HL generally occurs at an older age, and patients frequently present with B symptoms, organ involvement and unusual presentations such as bone-only disease (**Table 2**) (Yarchoan 2018). HIV-associated HL presents in an aggressive fashion, often with extranodal or bone marrow involvement.

Although the incidence of HL is 10-fold higher in patients with HIV than in the general population, the incidence has declined as a consequence of better HIV treatment (Bachanova 2016, Shanbhag 2018).

Table 2. Examples of Lymphoproliferative Disorders Strongly Associated with HIV Infection

Lymphoma Type	Key Immunohistochemical and Molecular Diagnostic Findings	Unique Features in Patients with HIV
Classic Hodgkin lymphoma	Often EBV+, Reed-Sternberg cells	Extranodal disease is frequently seen in patients with HIV, including presentations of bone-only disease; median age is higher than that for HL in the general population
Diffuse large B-cell lymphoma	CD20+, may have c-myc translocation	The most common lymphoma in patients with HIV; may have CNS involvement

CNS, central nervous system; EBV, Epstein-Barr virus; HL, Hodgkin lymphoma
Adapted from: Yarchoan 2018

The staging of HIV-associated lymphoma should include evaluation for CNS involvement. Cytologic analysis of the cerebrospinal fluid (CSF) may be associated with a high rate of false negative results; therefore, flow cytometric analysis of the CSF is useful in evaluating for leptomeningeal involvement.

Overall survival for patients with HIV-associated lymphoma has increased from < 20%, previous to three-drug antiretroviral therapy regimens, to > 80% at the present. Survival outcomes similar to those in the general population have been shown for patients with HIV-associated lymphomas when those patients are treated with full-dose regimens appropriate for the particular histologic type of lymphoma. Hematopoietic cell transplantation is feasible in patients with HIV with survival outcomes similar to those reported for the general population (Alvarnas 2016).

Because most HIV-associated tumors are caused by oncogenic viruses or other exogenous agents, they are potentially preventable. Early diagnosis and treatment of HIV with three-drug antiretroviral therapy plays an essential role in minimizing the risk of developing HIV-associated cancers.

The clinical presentation of AIDS-related lymphoma is very different from that seen in non-HIV patients with lymphoma. The HIV-infected individual with aggressive lymphoma usually presents with advanced-stage disease that is frequently extranodal. Common extranodal sites include:

- Bone marrow
- Liver
- Meninges
- Gastrointestinal tract

Unusual sites of disease include:

- Anus
- Heart
- Bile duct
- Gingiva
- Muscles

Treatment Approaches for Patients with HIV-associated Lymphoma

In patients with HIV-associated lymphoma, the clinical course is more aggressive and the disease is both more extensive and less responsive to chemotherapy than in other lymphoma patients. Immunodeficiency and cytopenias, common at the time of initial presentation, are exacerbated by the administration of chemotherapy. Treatment of lymphoma increases the risk of opportunistic infections, which further compromises the delivery of adequate treatment.

Treating patients with AIDS-related lymphoma is challenging due to the integration of therapy appropriate for the stage and histologic type of the disease with the limitations imposed by HIV infection. In addition to cancer treatment, components of an optimal treatment strategy include:

- Highly active antiretroviral therapy
- Prophylaxis for opportunistic infections
- Rapid recognition and treatment of infections

Managing patients with HIV and lymphoma is challenging for many reasons (**Figure 1**). Patients with HIV positivity and underlying immunodeficiency have poor bone marrow reserve, which compromises providing drugs at optimal dose intensity. The risk of infection may also lead to a decrease in drug dose. Lastly, chemotherapy itself compromises the immune system and increases the likelihood of opportunistic infection.

Challenges
- Underlying HIV syndrome
- Immune compromised status
- Multiple drug interactions
- Advanced age of the patient at diagnosis

Adapted from: Bachanova 2016

Figure 1. Challenges in treating patients with HIV-associated lymphoma

Castillo and colleagues (2015) used ABVD plus combination antiretroviral therapy to treat patients with HIV-associated, advanced-stage, classical HL and achieved 5-year progression-free survival and overall survival rates of 69% and 78%, respectively. Very good complete remission rates and 2-year progression-free survival rates were reported with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) combined with involved-field radiation in patients with HIV-associated HL (Hentrich 2012). In these patients, opportunistic infections are most often the cause of mortality (Berenguer 2008; Tanaka 2007). While the prognosis for this population has improved, cure rates remain lower than those achieved in patients without HIV infection (Bachanova 2016).

In HIV patients with DLBCL, both the R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) and dose-adjusted EPOCH (etoposide, prednisone, vincristine and doxorubicin) with ritixumab (R-EPOCH) regimens have been used to achieve effective remission (Hunter 2017).

The comprehensive management of patients with HIV and lymphoma requires input from diverse members of a multidisciplinary team. The therapeutic team should comprise a hematologist/oncologist, a specialist in HIV, and organ-specific specialists including healthcare professionals working in infectious disease, gastroenterology and hepatology, neurology and psychiatry/addiction management (Bachanova 2016).

Post-transplant Lymphoproliferative Disorders (PTLD)

Considerations

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphomas that are one of the most serious complications of solid organ transplant or allogeneic hematopoietic cell transplant and are largely driven by Epstein-Barr virus (EBV) (DeStefano 2018). PTLD after solid organ transplant are often of recipient origin whereas PTLD following allogeneic hematopoietic stem cell transplant (HSCT) are usually of donor origin (NCCN 2020b).

The failure of the immune system to launch a cytotoxic immune response against PTLD is multifactorial, comprising iatrogenic and physiological mechanisms (DeStefano 2018). Immunosuppressive agents diminish the quantity and quality of T cells, which makes them unable to produce cytokines essential for immune destruction.

The incidence of PTLD associated with either solid organ or HSCT varies, ranging from about 0.1% to 20% and increases with the number of risk factors present (**Table 3**). PTLD following solid organ transplant also varies depending on the type of organ transplanted and following allogeneic HCT varies depending on the degree of human leucocyte antigen (HLA) matching and the need for T-cell depletion protocol prior to transplantation. The presence of pre-transplant indolent lymphoproliferative disorders does not appear to raise the risk of PTLD (Strati 2016).

Table 3. Risk Factors for developing PTLD

Following solid organ transplant	Following hematopoietic stem cell transplant (HSCT)
EBV serology mismatch (recipient negative, donor positive); Type of transplanted organ (highest risks for multi-organ, bowel, lung, heart/lung transplants) Intensity of induction immunosuppression/type of immunosuppression; Use of ATG or anti-CD3 MAB, calcineurin inhibition with tacrolimus as primary immunosuppressive therapy; Use of azathioprine and new agents (belatacept) Active CMV	Unrelated or HLA-mismatched allografts; Use of ATG or anti-CD3 monoclonal antibody to prevent or treat GvHD; T-cell depletion of the allograft Reduced intensity conditioning Second transplantation

ATG, anti-thymocyte globulin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GvHD, graft versus host disease; MAB, monoclonal antibody
Source: NCCN 2020; DeStefano 2018

Diagnosis and Clinical Presentation

The clinical presentation of PTLD is characterized by a high incidence of extranodal disease, which may involve the gastrointestinal tract, solid allografts and the central nervous system. Histopathology and adequate immunophenotyping are essential to establish a diagnosis.

The diagnostic workup should include a physical examination, evaluation of performance status, laboratory assessments (CBC, metabolic panel, measurement of serum LDH), possibly bone marrow evaluation, information on history of immunosuppressive treatment and transplant course. Recommended imaging studies are chest/abdomen/pelvis CT and/or whole/body PET/CT scan. Cardiac status should be evaluated as well as testing for hepatitis B virus (HBV) and EBV. A differential diagnosis involves ruling out PTLD from an acute infection, graft versus host disease, graft rejection or malignancy relapse (DeStefano 2018).

Treatment Considerations in PTLD

Treatment will depend on the histological subtype of disease (6 subtypes have been identified) and should be individualized (NCCN 2020b). PTLD is relatively rare. Hence, there is scant clinical evidence available on optimal treatment and, therefore, enrollment in a clinical trial is highly recommended. The goal of treatment is to boost direct or immune-mediated killing of transformed lymphocytes (DeStefano 2018). Treatment should be initiated as soon as possible due to the risk of rapid tumor growth and multi-organ failure. The involvement of a multidisciplinary team in deciding on and implementing treatment is strongly advised.

The standard treatment of solid organ transplant-related PTLD and HSCT-related PTLD is shown in **Figure 2**. Reducing immunosuppression is often not feasible with HSCT-related PTLD due to the risk for graft versus host disease and graft rejection.

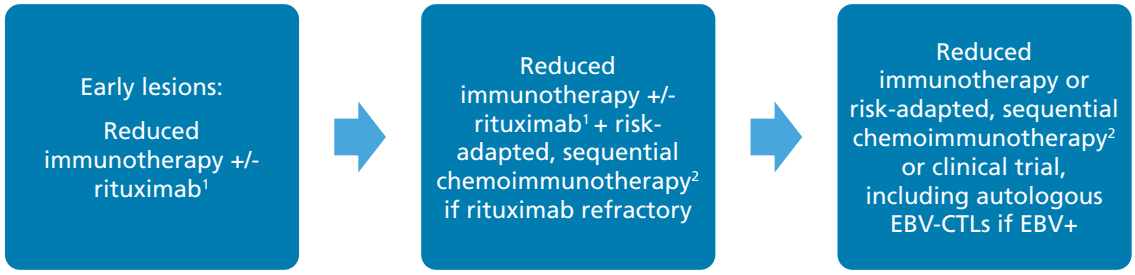

Figure 2a.

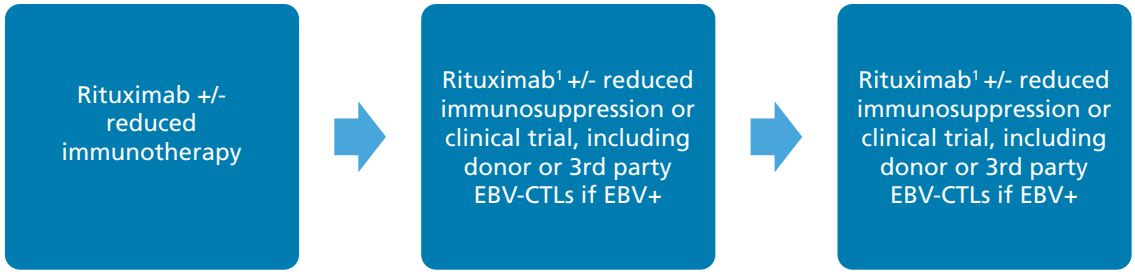

Figure 2b.

Figure 2. Treatment recommendations for solid organ transplant-related PTLD (a), and hematopoietic stem cell transplant-related PTLD (b) [1]Rituximab should only be used for CD20+ PTLD; [2]R-CHOP. Enrollment in a clinical trial is recommended for all patients with PTLD; CTL, cytotoxic T-lymphocyte; EBV, Epstein-Barr virus. Adapted from: DeStefano 2018

Retransplantation after diagnosis and treatment of PTLD is feasible in selected patients with PTLD following solid organ transplant. A waiting time of at least one year from treating PTLD to retransplantation is recommended.

Supportive care in this population includes prophylactic measures to prevent tumor lysis syndrome, infection prophylaxis and myeloid growth factor support for patients receiving chemotherapy (DeStefano 2018).

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Glossary of Terms*

Term	Definition
AIDS-defining illness	Certain serious and life-threatening diseases that occur in HIV-positive people are called „AIDS-defining" illnesses. When a person gets one of these illnesses, he or she is diagnosed with the advanced stage of HIV infection known as AIDS
Allogeneic hematopoietic cell transplantation	A procedure in which stem cells from a genetically matched, but not identical, donor are transfused into the recipient
Alopecia	The lack or loss of hair from areas of the body where hair is usually found. Alopecia can be a side effect of chemotherapy and radiation therapy
Anemia	A condition in which the hemoglobin level and usually the number of red blood cells (erythrocytes) are below normal range
Autologous stem cell transplantation	A procedure in which stem cells are harvested, stored and later infused into the same person
Azotemia	A higher than normal blood level of urea or other nitrogen-containing compounds. Evaluated using serum blood urea nitrogen (BUN) level.
Chimeric antigen (CAR T cells)	This therapy relies on the genetic manipulation of a patients' T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19
Complete metabolic response	A finding obtained using FDG PET-CT imaging demonstrating the disappearance of metabolic tumor activity in target and non-target lesions, marked by a decrease in tumor standardized uptake value to the level of surrounding normal tissue
Complete response (CR)	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission
Cytochemistry	The biochemistry of cells, especially that of the macromolecules responsible for cell structure and function; also describes a process of identification of the biochemical content of cells
Cytogenetics	The study of the structure and function of chromosomes
Cytomorphology	The morphology (form) of cells
Disease-free survival	A concept used to describe the period after successful treatment during which there are no signs and symptoms of the disease
Disseminated intravascular coagulation (DIC)	A condition in which small blood clots develop throughout the bloodstream, blocking small blood vessels. The increased clotting depletes the platelets and clotting factors needed to control bleeding; leads to excessive bleeding
Erythropoietin-stimulating agent	A drug that stimulates the bone marrow to produce red blood cells (erythrocytes)
Exosome	Extracellular vesicles that are released from cells upon fusion of an intermediate endocytic compartment, the multivesicular body, with the plasma membrane. This liberates intraluminal vesicles into the extracellular milieu and the vesicles thereby released are exosomes. Exosomes from cancer cells can be powerful mediators for promoting cancer cell survival and metastasis
Extramedullary sites	Situated or occurring outside the spinal cord or the medulla oblongata
Fatigue	Extreme tiredness despite getting enough sleep; interferes with the ability to carry out daily activities
Fluorescent in situ hybridization (FISH)	A test using special fluorescent dyes that attach to specific genes or parts of particular chromosomes. FISH identifies most chromosome changes (such as translocations) that are visible under a microscope in standard cytogenetic tests as well as some changes too small to be seen with usual cytogenetic testing. Can be used on peripheral blood or bone marrow or from tissues such as lymph node samples
Flow cytometry	A laboratory method used to detect, identify and count specific cells based on physical characteristics and/or markers called antigens on the cell surface or within cells that are unique to that cell type

Term	Definition
Genomic characterization Genetic profiling	A laboratory method used to evaluate genes and the way genes interact with each other and with the environment. Can be useful in identifying genetic predisposition to certain diseases or response to treatment
Genome/Genomics	The study of the complete set of DNA
Granulocyte colony-stimulating factor (G-CSF)	Glycoproteins that promote production of white blood cells (mainly granulocytes such as neutrophils), in response to infection; stimulates stem cells in the bone marrow to produce more of the particular white blood cells
Hematopoietic stem cells	The stem cells that give rise to other blood cells in a process called hematopoiesis
Human leukocyte antigen (HLA)	A gene complex encoding the major histocompatibility complex (MHC) proteins in humans. These cell-surface proteins are responsible for the regulation of the immune system
Immunconjugate therapy	Treatment that uses an immune substance, such as a monoclonal antibody, that is chemically linked to a cell-killing substance such as a toxin, radioisotope or drug. The immune substance targets certain types of cells and the linked substance kills the targeted cells without harming other cells
Immunohistochemistry	A laboratory method that uses antibodies to check for certain antigens in a tissue sample. The antibodies are usually linked to an enzyme or a fluorescent dye. After the antibodies bind to the antigen, the enzyme or dye is activated and the antigen can then be seen with a microscope. Used to diagnosis or differentiate types of cancer
Immunophenotyping	Classification of cancer cells according to the substances (antigens) on their surfaces. Leukemia cells can have different antigens depending on the type of cell in which the leukemia originated and the maturity of the cell
Immunosuppression	Suppression of the immune system and the ability to fight infections and other disease
Immunosuppressive therapy	Deliberate drug- or radiation-induced suppression of the immune system often in preparation for hematopoietic stem cell transplantation
Karyotype	Analysis of the chromosomes of the leukemic cells
Leukocyte	A blood cell produced in the bone marrow and found in peripheral blood and lymph tissue; cells are part of the immune system. Types are granulocytes, monocytes and lymphocytes
Leukocytosis	An increase in the number of white cells in the blood, especially during an infection
Leukopenia	Decrease in the number of leukocytes, which are the body's primary defense against infection
Lymphedema	A condition in which extra lymph fluid builds up in tissues and causes swelling. It may occur in an arm or leg if lymph vessels are blocked, damaged or surgically removed
Lymphoblast	A modified naïve lymphocyte with altered cell morphology. Refers to immature cells, which typically differentiate to form mature lymphocytes. In acute lymphoblastic leukemia (ALL) this term refers to malignant leukemic cells, precursors of the lymphocytes which multiply uncontrollably
Lymphoid cell	Any of the cells responsible for the production of immunity mediated by cells or antibodies and including lymphocytes, lymphoblasts and plasma cells
Macrophage	A type of white blood cell that surrounds and kills microorganisms, removes dead cells and stimulates the action of other immune system cells
Measureable/minimal residual disease (MRD)	Disease remaining after implementation of treatment
Miliary lesions	Innumerable, small 1-4 mm pulmonary nodules scattered throughout the lungs.
Monoclonal antibody	A type of protein made in the laboratory that can bind to substances in the body; developed to bind to only one substance

Term	Definition
Mucositis/Stomatitis	A complication of some chemotherapy/radiation therapy in which the lining of the digestive system becomes inflamed. Often seen as inflammation or irritation of the mucous membranes in the mouth
Myeloablative therapy	High-dose (most often) chemotherapy that kills cells in the bone marrow, including cancer cells. It lowers the number of normal blood-forming cells in the bone marrow and can cause severe side effects
Myeloblast	A unipotent stem cell which differentiates into the effectors of the granulocyte series; found in the bone marrow
Myelosuppression	A condition in which bone marrow activity is decreased, resulting in fewer erythrocytes, platelets and neutrophils.
Nadir	The lowest point. May refer, for example, to the lowest blood count after chemotherapy or the lowest concentration of a drug in the body
Natural killer cells	A lymphocytes able to bind to certain tumor cells and virus-infected cells without the stimulation of antigens, and destroy them by the insertion of granules containing perforin
Neoplastic cells	Cancer/malignant cells
Neutropenia	Decrease in the number of granulocytes, which are white blood cells, and provide the primary defense against infection
Oncogene	A gene that is a mutated (changed) form of a gene involved in normal cell growth. Oncogenes may cause the growth of cancer cells. Mutations in genes that become oncogenes can be inherited or caused by being exposed to substances in the environment that cause cancer
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment that patients diagnosed with the disease are still alive; used in clinical trials to measure the efficacy of a treatment
Pancytopenia	Reduction in the number of erythrocytes, platelets and granulocytes
Phenotype	The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment
Polymerase chain reaction (PCR)	A laboratory technique used to make multiple copies of a segment of DNA; very precise and can be used to amplify, or copy, a specific DNA target from a mixture of DNA molecules
Progenitor cells	A biological cell that, like a stem cell, has a tendency to differentiate into a specific type of cell, but is already more specific than a stem cell and is pushed to differentiate into its "target" cell
Progression-free survival (PFS)	The length of time during and after cancer treatment that a patient lives with the disease but it does not progress. Used in clinical trials to evaluate how well a new treatment works
Proto-oncogene	A gene involved in normal cell growth. Mutations in a proto-oncogene may cause it to become an oncogene, which can cause the growth of cancer cells
Quality of Life (QoL)	An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns
Radiation cystitis	Inflammation of the lining of the bladder caused by radiation therapy to the pelvis, including the bladder. Symptoms may dissipate after radiation therapy is stopped
Radiation dermatitis	A skin condition that is a common side effect of radiation therapy. The affected skin becomes painful, red, itchy and blistered
Residual disease	Quality of malignant cells remaining after the administration of a treatment. To determine this, very different specific laboratory techniques may be used

Term	Definition
Thrombocytopenia	A condition in which there is a lower-than-normal number of platelets in the blood; may cause easy bruising and bleeding from wounds or bleeding in mucous membranes
Tumor lysis syndrome (TLS)	A condition that occurs when a large number of cancer cells die within a short period, releasing their contents in to the blood
Tumor suppressor gene	A type of gene that makes a protein called a tumor suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer. Also called antigene
Vesicant extravasation	The leakage of certain drugs called vesicants out of a vein into the tissue around it. Vesicants cause blistering and other tissue injury that may be severe and can lead to tissue necrosis
Xerostomia	Dry mouth, occurs when there is insufficient saliva. Can be caused by some types of chemotherapy and radiation to the head/neck

*The terms listed in this glossary are not necessarily specific to lymphomas. Some terms refer to general concepts in the diagnosis, treatment and management of cancers and other diseases or conditions.

Resources

Website Resources for Healthcare Professionals	
American Society of Clinical Oncology (ASCO) Cancer Survivorship Compendium asco.org/survivorship	Practice tools and resources to help healthcare professionals in cancer care improve services for patients who have completed curative treatment or who have transitioned to maintenance or prophylactic therapy. Topics covered included fertility counseling, managing psychosocial effects of cancer, financial concerns as well as guidance regarding diet and exercise
BC Cancer www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#g-content	Concise, current information on drugs used in oncology. Also provides patient information on drugs.
Cancer Research UK www.cancerresearchuk.org/	Provides information about symptoms, risk factors, incidence statistics, treatment, and trials for non-Hodgkin lymphoma
Website Resources for Patients and Families and Healthcare Professionals	
American Cancer Society (ACS) www.cancer.org	Extensive source of information for cancer patients and caregivers
American Society of Clinical Oncology (ASCO) Cancer Survivorship Compendium www.cancer.net/survivorship	Information on what to expect after treatment ends, managing late effects of treatment, coping with life after cancer and dealing with a recurrence
Centers for Disease Control and Prevention Cancer Survivors: www.cdc.gov/cancer/survivors/index.htm	Information on an array of topics for patients and survivors, cancer caregivers and healthcare providers
Facebook	Several helpful patient groups exist, such as "Living with follicular lymphoma"
Journey Forward https://www.journeyforward.org/category/cancer/	Information for cancer survivors on life after cancer treatment, self-care after cancer, management of cancer/treatment symptoms
Livestrong https://www.livestrong.org/	A variety of tools and resources to help ease the challenges of a cancer diagnosis
Lymphoma Coalition www.lymphomacoalition.org/	A worldwide network of lymphoma patient groups; provides a comprehensive database with referral to local support groups
Lymphoma Association www.lymphomas.org.uk/ New name: Lymphoma Action	Specializes in providing information and support to anyone affected by lymphoma (i.e., patients, family, care givers, friends). Services at this interactive website include a helpline, a wide-range of free patient literature, information on local support groups and educational resources
Lymphoma Action www.lymphoma-action.org.uk/ Lymphoma Action is the new name of the Lymphoma Association, is country specific.	Provides information literature and support to patients with lymphoma and runs a "buddy" scheme that matches newly diagnosed patients with a patient who has already been through a similar diagnosis (UK site)
Lymphoma Information Network www.lymphomainfo.net/	Offers comprehensive patient information on lymphoma and its treatment
Lymphoma Research Foundation www.lymphoma.org/	Offers a wide-range of educational programs and free publications for people with lymphoma including disease-specific guides and disease-specific and treatment-specific fact sheets
Leukemia & Lymphoma Society www.lls.org	Offers online educational materials and web-based programs
National Cancer Institute (NCI) Office of Cancer Survivorship https://cancercontrol.cancer.gov/ocs	Extensive source of information on the topic of cancer survivorship for survivors and caregivers, healthcare professionals, researchers and advocates
National Comprehensive Cancer Network https://www.nccn.org/	Extensive source of practice guidelines for healthcare professionals. Guidelines for patients are meant to help patients with cancer talk with their physicians about the best treatment options for their disease

Resources

Country-specific resources

Macmillan Cancer Support www.macmillan.org.uk	Offers medical, psychological, and financial support to patients diagnosed with cancer (UK site)
Lymphome.ch www.lymphome.ch	A Swiss organization which aims to raise awareness about lymphoma and provide information and support to patients and their families
France Lymphome Espoir www.francelymphomeespoir.fr/	A French association of patients with lymphoma which aims to assist and inform about the disease and treatment
American Cancer Society (ACS) www.cancer.org	Extensive source of information for cancer patients and caregivers
Deutsche Leukämie & Lymphom Hilfe e.V www.leukaemie-hilfe.de/startseite.html	A German organization dedicated to providing support, including education, to patients with leukemia and lymphoma
Patiëntenvereniging voor Lymfomen www.lymfklierkanker.be/nl/	A Dutch-language organization that offers support to patients and family by providing information on lymphoma and its treatment. The organization offers information sessions, symposia, patient meetings and works with hematologists at different university hospitals in Belgium.

The Resources are not comprehensive; it is a selection of what is available.

Notes

HNHCP
Haematology Nurses & Healthcare Professionals Group

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