Chapter 155: Lymphomas

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UPDATE SUMMARY

Update Summary

March 1, 2023

The following updates to this chapter were made:

- Hodgkin Lymphoma, Treatment: Hodgkin Lymphoma, Classic Hodgkin Lymphoma, Treatment of Advanced-Stage Disease: included updated survival data for A+AVD versus ABVD
- Non-Hodgkin Lymphoma, Treatment: Non-Hodgkin Lymphoma, Follicular Lymphomas, Treatment of Advanced Disease (Stages II Bulky, III, and IV): removed radioimmunotherapy subsection as it is removed from guidelines
- Non-Hodgkin Lymphoma, Treatment: Non-Hodgkin Lymphoma, Follicular Lymphomas, Treatment of Advanced Disease (Stages II Bulky, III, and IV): removed idelalisib, duvelisib, and umbralisib as they are no longer approved
- Non-Hodgkin Lymphoma, Treatment: Non-Hodgkin Lymphoma, Follicular Lymphomas, Treatment of Advanced Disease (Stages II Bulky, III, and IV): added mosunetuzumab under T-cell-mediated therapy
- Non-Hodgkin Lymphoma, Treatment: Non-Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Treatment of Refractory or Relapsed Disease: updated information regarding CAR T-cell therapy
- Non-Hodgkin Lymphoma, Treatment: Non-Hodgkin Lymphoma, Mantle Cell Lymphoma: added pirtobrutinib
- Revision of self-assessment question 12 to focus on lenalidomide rather than the radioimmunoconjugate ^{90}Y-ibritumomab tiuxetan

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 64, Lymphomas.

KEY CONCEPTS

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1. With all stages and risk groups of Hodgkin lymphoma, restaging PET-CT following 8 to 12 weeks of chemotherapy will further guide the patient-specific treatment plan.

2. Patients with early-stage Hodgkin lymphoma should be treated with combination chemotherapy with or without involved-site radiation.

3. Combination chemotherapy with doxorubicin (Adriamycin®), bleomycin, vinblastine, and dacarbazine (ABVD) is the primary treatment for patients with advanced-stage Hodgkin lymphoma. Patients with advanced unfavorable disease may be treated with more aggressive regimens, which are associated with a higher risk of secondary malignancies.

4. Some patients with Hodgkin lymphoma will be refractory to initial therapy or will have a recurrence following complete remission. Response to salvage therapy depends on the extent and site of recurrence, previous therapy, and duration of initial remission. High-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) should be considered in patients with refractory or relapsed disease.

5. The current classification system for non-Hodgkin lymphoma (NHL) is the World Health Organization (WHO) classification system, which classifies NHLs into specific disease entities, defined by a combination of morphology, immunophenotype, genetic features, and clinical features.

6. As compared with Hodgkin lymphoma, the clinical presentation of NHL is more variable because of disease heterogeneity and more frequent extranodal involvement.

7. The Ann Arbor staging system correlates poorly with prognosis in NHL because the disease does not spread through contiguous lymph nodes and often involves extranodal sites.

8. Several prognostic models have been developed to estimate prognosis in patients with NHL. The International Prognostic Index (IPI) score is a well-established model for patients with aggressive NHL. The Follicular Lymphoma International Prognostic Index (FLIPI) is a similar model for patients with follicular and other indolent lymphomas.

9. The clinical behavior and degree of aggressiveness can be used to categorize NHL into indolent and aggressive lymphomas. Patients with indolent lymphoma usually have relatively long survival, with or without aggressive chemotherapy. Although these lymphomas respond to a wide range of therapeutic approaches, few if any of these patients are cured of their disease. In contrast, aggressive lymphomas are rapidly growing tumors and patients have a short survival if appropriate therapy is not initiated. Most patients with aggressive lymphomas respond to intensive chemotherapy and many are cured of their disease.

10. Patients with localized follicular lymphoma can be cured with radiation therapy alone. Advanced follicular lymphoma is not curable, and many treatment options are available, including watchful waiting, radiation therapy, anti-CD20 monoclonal antibodies, chemoimmunotherapy, lenalidomide, PI3K inhibitors, an EZH2 inhibitor, CAR T-cell therapy, and high-dose chemotherapy with HSCT.

11. Patients with localized aggressive lymphomas can be cured with several cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin [Hydroxydaunorubicin], vincristine [Oncovin®], prednisone) chemotherapy and involved-field irradiation. Patients with bulky stage II, stage III, or stage IV aggressive lymphomas can be cured of their disease with R-CHOP chemotherapy.

12. Conventional-dose salvage therapy can induce responses in patients with aggressive lymphomas who relapse, but long-term survival and cure are uncommon. Some patients with aggressive lymphoma who relapse and respond to salvage therapy can be cured with high-dose chemotherapy and autologous HSCT.

BEYOND THE BOOK

BEYOND THE BOOK

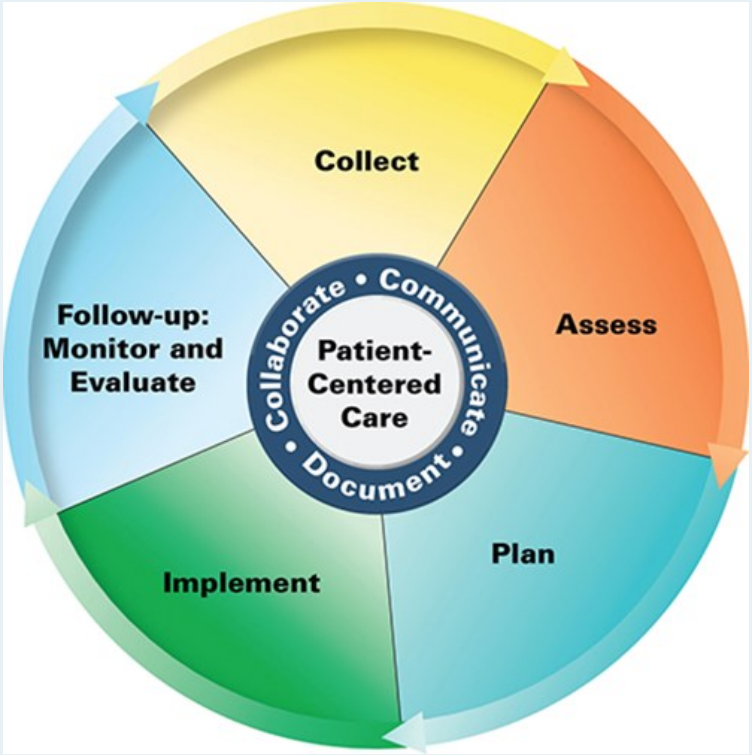
1. Read the patient information sheets from the American Society of Clinical Oncology at Cancer.Net on the diagnosis of Hodgkin and non-Hodgkin lymphoma (https://tinyurl.com/y2rr48nq and https://tinyurl.com/wm8emum). These information sheets briefly describe the various procedures used to diagnose lymphoma and will help students to understand how lymphoma is diagnosed.
2. Search the database of FDA-approved drug products and identify drugs that have been approved by the FDA in the last 12 months for lymphoma. Select one drug and compare the mechanism of action and its role in therapy with existing treatments that carry the same indication. Discuss advantages of this new drug over current therapies and challenges posed when using this new medication.

INTRODUCTION

Lymphomas are a heterogeneous group of malignancies that arise from malignant transformation of immune cells that reside predominantly in lymphoid tissues. They most commonly present as a solid tumor but can sometimes present as circulating tumor cells in peripheral blood. The differing histology of lymphoma cells has led to classification of Hodgkin lymphoma (Reed–Sternberg cells) or non-Hodgkin lymphoma (NHL) (B- or T-cell lymphocyte markers). NHLs are further classified into distinct clinical entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features. Chemotherapy is the mainstay of treatment in patients with lymphoma, especially those with widespread disease. Overall cure rates are high for many subtypes of lymphomas, even when patients present with advanced disease.

PATIENT CARE PROCESS

Patient Care Process for Lymphoma



Collect

- Patient characteristics (eg, age, sex, pregnant, smoking history)

- Patient medical history (personal and family)
- Current medications including OTC aspirin/NSAID use, herbal products, dietary supplements
- Objective data
  - Height and weight to calculate body surface area (BSA)
  - Labs include complete blood count (CBC), complete metabolic panel which includes liver function tests, LDH, pregnancy test for women with reproductive potential
  - Baseline assessment of cardiac ejection fraction by ECHO or MUGA if treatment with anthracycline is planned
  - Baseline assessment of pulmonary function (pulmonary function test including diffusing capacity of lungs for carbon monoxide—DLCO) if treatment with bleomycin is planned
  - Lymphoma-specific immunophenotyping, cytogenetics, such as CD20, CD30, t(11:14), t(14;18)
  - Stage and prognostic score (eg, IPS, IPI, FLIPI)

Assess

- Comorbid illnesses that may affect drug therapy selection (baseline neuropathy, CHF, renal or hepatic dysfunction)
- Potential for drug-drug interactions (particularly with oral agents such as idelalisib or ibrutinib)
- Patient's risk of tumor lysis syndrome based on disease, planned therapy, tumor burden, and renal function
- Ability to self-care, family/social support
- Financial challenges—copays, coinsurance, specialty pharmacy medication access
- Birth control and fertility options if the patient is of childbearing age (male and female)
- Emotional status (eg, anxiety, depression)
- Need for central venous access
- Access and availability of eligible clinical trials

Plan*

- Logistics of the treatment plan (inpatient, outpatient, daily oral medication) and monitoring plan
- Patient education (eg, goals and purpose of treatment, treatment schedule, duration/number of treatment cycles, drug-specific information, medication administration)
- Self-monitoring for toxicities, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, dietician, navigator, behavioral health, integrative health, palliative/supportive care)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Obtain consent for planned treatment

- Use motivational interviewing and coaching strategies to maximize adherence
- Write, order, or review therapy orders to ensure appropriate dosing, supportive care therapies (eg, nausea/vomiting, infection prevention, prevention of hypersensitivity reactions)
- Schedule follow-up (eg, oral therapy medication therapy management, adherence assessment, symptom management)
- Connect patient to resources such as support groups, educational websites, community resources, social worker

Follow-up: Monitor and Evaluate

- Survivorship teaching and follow-up with focus on monitoring for long-term toxicities
- Patient adherence to treatment plan using multiple sources of information
- Imaging studies to be ordered for appropriate follow-up
- Necessary vaccines following stem-cell transplant

Collaborate with patients, caregivers, and other healthcare professionals.

HODGKIN LYMPHOMA

Hodgkin lymphoma is one of the most curable forms of cancer. Although initial reports of Hodgkin lymphoma demonstrated the disease to be uniformly fatal, an impressive 80% of patients can be cured today with recommended treatments.[1] Some of the keys to the success of the treatments for Hodgkin lymphoma include the appropriate use of multidrug chemotherapy regimens with differing mechanisms of action and toxicities and treatment with full doses of chemotherapy and on schedule whenever possible. It is also common to use radiation therapy in the treatment schema. However, the success of treatment has not been without cost. The treatment programs are intense, technically demanding, and associated with considerable acute toxicity and long-term complications. The long-term effects, particularly secondary malignancies, account for higher cumulative mortality than Hodgkin lymphoma 15 to 20 years after treatment. Long-term toxicities with standard chemotherapy regimens have been more fully documented in recent years and are shaping future therapies.[2,3]

Hodgkin lymphoma is named after Thomas Hodgkin, who first described seven cases of a mysterious disease of the lymph system in 1832. Although Hodgkin lymphoma was not the first cancer to be described, it was one of the first cancers to have methodical investigational treatments that ultimately lead to successful outcomes.[3]

Since many factors influence the prognosis of patients with Hodgkin lymphoma, treatment plans must be personalized for each patient. The staging for Hodgkin lymphoma uses the Ann Arbor Staging Classification where the “A” refers to the absence of B symptoms, and “B” refers to the presence of B symptoms. Beyond the stage of the disease, certain factors have been associated with a poor prognosis (unfavorable risk). Several research groups have defined these unfavorable factors, and the International Prognostic Score (IPS) is used clinically to predict an individual’s risk of recurrence.

Epidemiology and Etiology

Hodgkin lymphoma represents less than 1% of all known cancers in the United States. About 8,830 new cases of Hodgkin lymphoma were diagnosed in the United States in 2023, and 900 deaths associated with Hodgkin lymphoma will occur during this same period.[4] Hodgkin lymphoma occurs slightly more frequently in males than in females. It exhibits bimodal distribution in industrialized countries; the first peak occurs in young adults and the second smaller peak occurs after the age of 50 years.[2,3] The 5-year overall survival for all stages of Hodgkin lymphoma is about 85%.[1] Death from recurrent Hodgkin lymphoma is less than those from all other causes 15 years after treatment.

The etiology of Hodgkin lymphoma is unknown, but laboratory and epidemiologic evidence supports infectious exposure as a potential cause.[2,3] Studies suggest an increased risk of Hodgkin lymphoma in patients who have been infected with the Epstein-Barr virus (EBV), and many patients experience EBV activation even before the onset of Hodgkin lymphoma. EBV is found in about 40% of all classical Hodgkin lymphoma cases, and it is

frequently observed in cases of mixed cellularity and lymphocyte-depleted Hodgkin lymphoma. Reed–Sternberg cells (large, bilobate, multinuclear cells looking like “owl eyes”), the malignant cells in Hodgkin lymphoma, are linked to EBV. Individuals who are immunosuppressed, such as patients with congenital immunosuppression, solid-organ transplant recipients, and human immunodeficiency virus (HIV)-infection, are also at much higher risk of developing Hodgkin lymphoma. Although the risk of developing Hodgkin lymphoma is up to 25-fold greater in patients with HIV, the CD4 level may be low or within the normal range at diagnosis. Almost all cases of Hodgkin lymphoma in HIV-infected individuals are EBV positive and are most commonly the lymphocyte-deplete subtype of Hodgkin lymphoma. Hodgkin lymphoma is not an AIDS-defining illness.

Genetic factors are also associated with an increased risk of Hodgkin lymphoma. The strongest evidence comes from identical twin studies, which show that the unaffected identical twin has almost a 100-fold increase in risk.

Pathophysiology

Hodgkin lymphoma is a clonal malignant lymphoid disease of transformed B-lymphocytes. The malignant cell in Hodgkin lymphoma is the Reed–Sternberg cell, named after Dorothy Reed and Carl Sternberg, who were credited with the first definitive microscopic description of Hodgkin lymphoma.[2] Single-cell polymerase chain reaction and DNA microarray analyses indicate that nearly all classic Hodgkin lymphoma cases and all nodular lymphocyte-predominant Hodgkin lymphomas (NLPHLs) have immunoglobulin gene rearrangements, which indicates a germinal center or postgerminal center of B-cell origin. Interestingly, nearly all Reed–Sternberg cells of classical Hodgkin lymphoma fail to express B-cell specific cell surface proteins.

B-cell transcriptional processes are disrupted during malignant transformation, which prevents B-cell surface marker expression and production of immunoglobulin messenger ribonucleic acid. The normal cellular consequence of failure to express immunoglobulin is apoptosis, but because of alterations in the normal apoptotic pathways, cell survival and proliferation are favored. Reed–Sternberg cells overexpress nuclear factor-κB, which is associated with cell proliferation and antiapoptotic signals. Infections with viral and bacterial pathogens upregulate nuclear factor-κB and consequently are hypothesized to be involved with the etiology of Hodgkin lymphoma.[2] This hypothesis is supported by the presence of EBV in many Hodgkin lymphoma tumors, but not all tumors are associated with EBV. Another signaling pathway, Janus kinase–signal transduction and transcription (JAK–STAT), is also active in Hodgkin lymphoma.[2] As molecular techniques continue to improve, our understanding of the pathophysiology of Hodgkin lymphoma will also improve.

The histopathologic classification of Hodgkin lymphoma has undergone numerous changes over the past three decades. The current classification system is the 2016 World Health Organization (WHO) classification (Table 155-1).[5] This classification divides Hodgkin lymphoma into two major groups: classical Hodgkin lymphoma and NLPHL, which constitute about 95% and 5% of cases, respectively. Classic Hodgkin lymphoma is further divided into four subtypes: nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich. The subtypes in these classifications are based on characteristics of the Reed–Sternberg cell, the surrounding cells, and the tissue. Nodular sclerosis has features that make it distinct from the other three subtypes, which represent a continuum of background cellularity, with lymphocyte-predominance being the most cellular and lymphocyte-depletion being the least cellular. Typical immunophenotype for classical Hodgkin lymphoma includes $CD15^+$, $CD30^+$, $PAX\text{-}5^+$ (weak), $CD3^-$, $CD20^-$, $CD45^-$, and $CD79a^-$. NLPHL is separated because of its distinct immunophenotype: $CD15^-$, $CD20^+$, $CD30^-$, and $CD45^+$ (the opposite of classical Hodgkin lymphoma). With the use of extensive staging, sophisticated radiotherapy, and effective combination chemotherapy, the prognostic value of these subtypes is becoming less clear. The true value of understanding these subtypes is likely tied to the pathogenesis of the disease and its potential prevention in the future.

TABLE 155-1

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2016)

B Cell	Mature T and NK Cells	Hodgkin Lymphoma
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma B-cell prolymphocytic leukemia Lymphoplasmacytic lymphoma Splenic marginal zone B-cell lymphoma (± villous lymphocytes) Hairy cell leukemia **Plasma cell myeloma/plasmacytoma** **Extranodal marginal zone B-cell lymphoma of MALT type** **Mantle cell lymphoma** **Follicular lymphoma** Nodal marginal zone B-cell lymphoma (± monocytoid B cells) **Diffuse large B-cell lymphoma (DLBCL)** Germinal center B-cell type Activated B-cell type **Burkitt lymphoma**	T-cell prolymphocytic leukemia T-cell granular lymphocytic leukemia Aggressive NK-cell leukemia Adult T-cell leukemia/lymphoma (HTLV-I+) Extranodal NK/T-cell lymphoma, nasal type Enteropathy-associated T-cell lymphoma Hepatosplenic γ δ T-cell lymphoma Subcutaneous panniculitis-like T-cell lymphoma **Mycosis fungoides/Sézary syndrome** **Anaplastic large cell lymphoma, primary cutaneous type** **Peripheral T-cell lymphoma, not otherwise specified (NOS)** **Angioimmunoblastic T-cell lymphoma** **Anaplastic large cell lymphoma, primary systemic type**	Nodular lymphocyte-predominant Hodgkin lymphoma Classical Hodgkin lymphoma Nodular sclerosis classical Hodgkin lymphoma Lymphocyte-rich classical Hodgkin lymphoma Mixed cellularity classical Hodgkin lymphoma Lymphocyte-depleted classical Hodgkin lymphoma

HTLV, human T-cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer; WHO, World Health Organization.

Note: Not all subtypes are listed. **Malignancies in bold occur in at least 1% of patients**.

(Adapted from Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. World Health Organization; 2008.)

Clinical Presentation

CLINICAL PRESENTATION: Hodgkin Lymphoma

General

- Most patients with Hodgkin lymphoma have lymph node involvement in the supradiaphragmatic and mediastinal areas.

Symptoms

- Fatigue, malaise, and pruritus.
- About 25% of all patients present with fever, night sweats, and weight loss (ie, B symptoms), and up to 50% of patients with advanced disease.

Signs

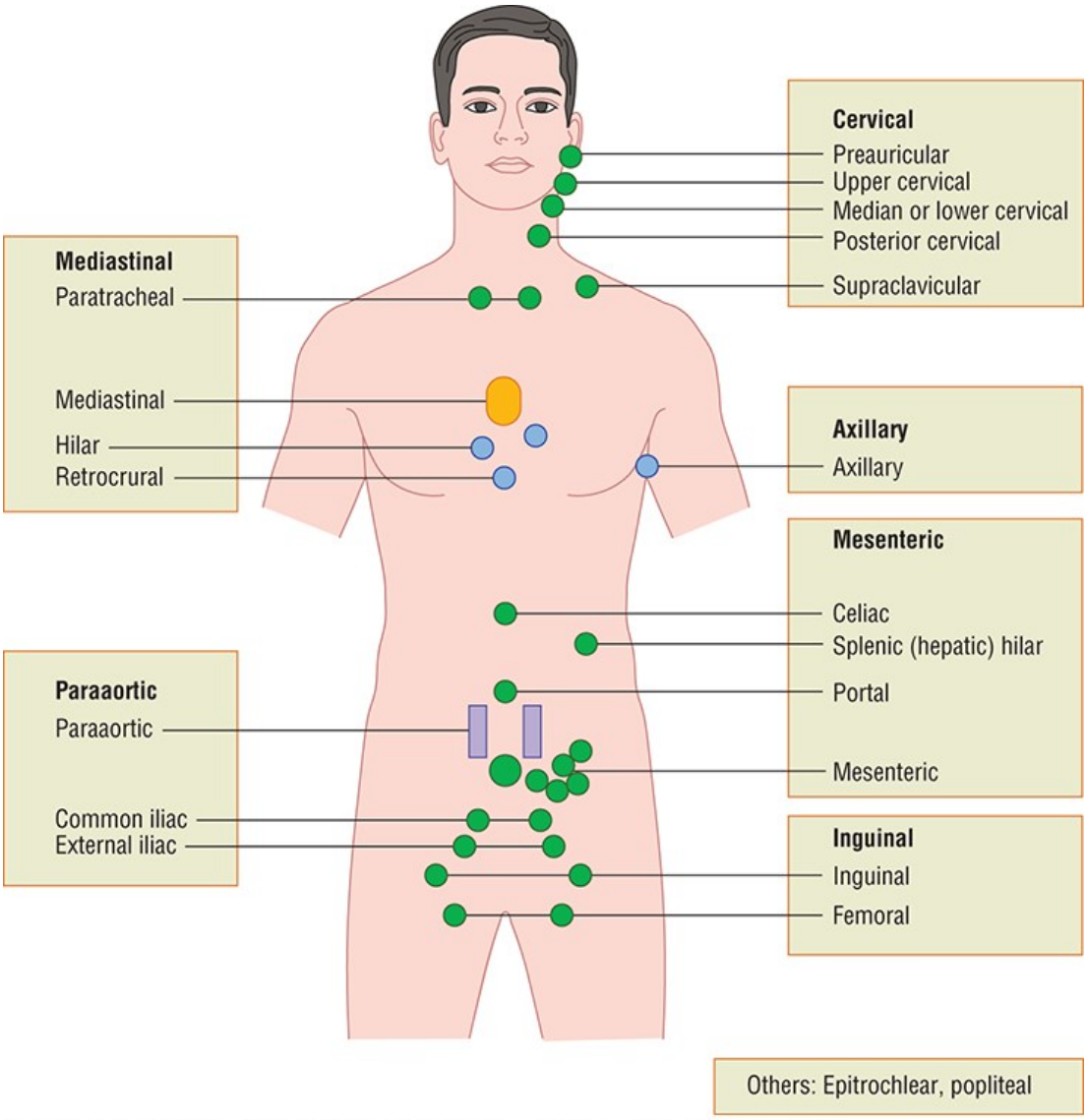
- Enlarged lymph node, which may present as painless and rubbery.

Most patients with Hodgkin lymphoma present with a painless, rubbery, enlarged lymph node in the supradiaphragmatic area and commonly have

mediastinal nodal involvement. Lymphadenopathy may come and go, but the persistence of lymphadenopathy for more than 2 months warrants evaluation. Hodgkin lymphoma is occasionally diagnosed in an asymptomatic patient who has a mediastinal mass found with chest radiography or another imaging procedure. Asymptomatic adenopathy of the inguinal and axillary regions may be present at diagnosis but is less common (Fig. 155-1).[2,3] Patients can also present with constitutional symptoms (B symptoms) before the discovery of lymph node enlargement, and these symptoms include fever greater than 38°C (100.4°F), drenching night sweats, and weight loss greater than 10% within 6 months of diagnosis. At diagnosis, these symptoms may appear in about 25% of all patients and up to 50% of patients with advanced disease. Patients may also experience other nonspecific symptoms including pruritus, fatigue, and development of pain after alcohol consumption at sites where nodes are involved.[3] Extranodal manifestations, such as bowel or hepatic involvements, are much less common in Hodgkin lymphoma than NHL.[2]

FIGURE 155-1

Areas of lymph nodes used in the staging of Hodgkin and non-Hodgkin lymphoma. Each rectangle corresponds to a nodal area.



Diagnosis, Staging, and Prognostic Factors

Diagnostic and staging procedures are based on recommendations made at the Ann Arbor and Cotswolds conferences and new scientific advances. The diagnosis and pathologic classification of Hodgkin lymphoma can only be made by review of a biopsy (preferably an excisional biopsy) of the enlarged node by an expert hematopathologist.

In addition to a careful physical examination, routine laboratory tests including a complete blood count, complete metabolic panel to assess renal and hepatic function, lactate dehydrogenase (LDH), and erythrocyte sedimentation rate (ESR) are helpful in treatment planning and aid in prognosis. Pregnancy test and HIV status should be assessed. Computed tomography (CT) scans of the chest, abdomen, and pelvis are routinely performed. Furthermore, positron emission tomography (PET) plays an important role in the initial staging of Hodgkin lymphoma, as it has shown high sensitivity and specificity in the staging of the disease response to treatment.[6] The use of integrated PET-CT has further improved the staging of Hodgkin lymphoma given that it can provide more sensitive and specific imaging as compared with each imaging alone. Bone marrow biopsy is now recommended only in patients with cytopenias and a negative PET.

Staging can be based on clinical or pathologic findings. The clinical stage is based on all noninvasive procedures (history, physical examination, laboratory tests, and radiologic findings), whereas the pathologic stage is based on the biopsy findings of strategic sites (bone marrow, spleen, and abdominal nodes). Patients with extranodal disease (bone marrow, bone, or Waldeyer ring) contiguous to involved nodes are classified with the subscript “E” in the Cotswolds staging system.

The Ann Arbor staging classification, which was developed at the 1970 Ann Arbor conference, has proven to be a good schema. At the Cotswolds meeting in 1989, the Ann Arbor classification was modified to incorporate new diagnostic techniques (eg, CT and magnetic resonance imaging), and the understanding that prognosis is associated with the bulk of the disease and the number of involved nodal sites (Fig. 155-1, Table 155-2).[3] After careful staging, about one-half of patients have localized disease (stages I, II, and II_E) and the remainder have advanced disease (stage III or IV). About 10% to 15% present with metastatic disease (stage IV). Hodgkin lymphoma follows a predictable pattern of nodal spread that is not seen with the NHLs.[3]

TABLE 155-2

The Ann Arbor Staging Classification of Hodgkin Lymphoma

Stage I	Involvement of a single lymph node region or structure (I) or of a single extralymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (II_E). The number of nodal regions involved should be indicated by a subscript (eg, II_2)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an extralymphatic organ or site (III_E) or by involvement of the spleen (IIIS) or both ($IIIS_E$). III_1: with or without splenic, hilar, celiac, or portal node involvement. III_2: with paraaortic, iliac, or mesenteric node involvement
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement A—No symptoms B—Fever, night sweats, weight loss (>10%) X—Bulky disease >One-third of the width of the mediastinum >10-cm maximal dimension of nodal mass E—Involvement of extralymphatic tissue on one side of the diaphragm by limited direct extension from an adjacent, involved lymph node region S—Involvement of the spleen CS—Clinical stage PS—Pathologic stage

Patient prognosis is predominately driven by age and amount of disease. Patients older than 65 to 70 years have a lower cure rate than younger patients. The difference in cure rates may be related to the higher prevalence of comorbid diseases and decreased organ function in older patients, which impairs their ability to tolerate intensive chemotherapy. Stage is a dominant factor in predicting survival; patients with limited-stage disease (stages I-II) have a 90% to 95% cure rate, while those with advanced disease (stages III-IV) have only a 60% to 80% cure rate.[2,3]

Seven adverse prognostic factors with similar impact on survival (each factor reduced survival by 7%-8% per year) have been identified through an international collaborative effort. These factors can be combined to generate an IPS that can be used to predict progression-free and overall survival (Table 155-3).[7]

TABLE 155-3

The International Prognostic Factors Project Score for Advanced Hodgkin Lymphoma

Risk Factors
Serum albumin (<4 g/dL [40 g/L])
Hemoglobin (<10.5 g/dL [105 g/L; 6.52 mmol/L])
Male gender
Stage IV disease
Age (≥45 years)
White blood cell (WBC) count (≥15,000 cells/mm^3 [15×10^9/L])
Lymphocytopenia (<600 cells/mm^3 [0.6×10^9/L] or <8% of WBC count)

Number of Factors	Freedom from Progression*	Overall Survival*
0	84 ± 4	89 ± 2
1	77 ± 3	90 ± 2
2	67 ± 2	81 ± 2
3	60 ± 3	78 ± 3
4	51 ± 4	61 ± 4
≥5	42 ± 5	56 ± 5

*Percentage of patients at 5 years.

Data from Reference 7.

Treatment: Hodgkin Lymphoma

Desired Outcomes

The current goal in the treatment of Hodgkin lymphoma is to maximize curability while minimizing short- and long-term treatment-related complications. According to the Surveillance, Epidemiology, and End Results (SEER) database, the 5-year age-adjusted relative survival is greater than 80%.[1] Therefore, the initial treatment goal for all stages of Hodgkin lymphoma is the cure.

General Approach

Combination chemotherapy is the primary treatment modality for most patients with Hodgkin lymphoma. In general, patients of all stages are initially treated with combination chemotherapy for about 8 to 12 weeks (depending on the regimen) and then restaged with PET-CT. Three combination chemotherapy regimens are primarily used for the initial treatment of classical Hodgkin lymphoma: ABVD, BEACOPP (bleomycin, etoposide, doxorubicin [Adriamycin®], cyclophosphamide, vincristine [Oncovin®], procarbazine, and prednisone), and A-AVD (brentuximab vedotin [Adcetris®], doxorubicin [Adriamycin®], vinblastine, and dacarbazine). Depending on the initial radiographic response from the restaging, further chemotherapy with or without radiation is planned. For patients with refractory or recurrent disease, salvage therapy consists of multi-agent chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT).[2,3]

Radiation is often an integral part of the treatment plan. Selected patients with early-stage disease (usually nodular lymphocyte-predominant histology) can receive radiation as the only treatment modality, whereas most other patients with early-stage disease may receive chemotherapy and radiation depending on the initial bulk of disease and the response to chemotherapy alone. Although radiation is a local therapy, many patients with advanced disease will also receive radiation therapy to residual or bulky disease sites after chemotherapy. Many different radiation techniques targeting different radiation fields have been used over the last few decades, including involved-field radiation (IFRT), extended-field radiation, subtotal nodal irradiation, and total nodal irradiation. The major concern with radiation therapy is its long-term effects, particularly on organs at risk, such as cardiovascular disease and secondary malignancies that commonly occur in the lung, breast, gastrointestinal tract, and connective tissue.[8] Involved-site radiation therapy (ISRT) and involved-node radiation therapy are now being used as alternatives to the classic IFRT, and both define a smaller field than IFRT. ISRT targets the nodal sites and extranodal extensions involved at diagnosis but spares adjacent uninvolved organs when lymphadenopathy regresses after chemotherapy and ISRT. Additional techniques help refine the volume of radiation delivered to the intended sites such as 4D-CT simulation planning, intensity-modulated radiation therapy, image-guided radiation therapy, and respiratory gating.[9]

Although multiple treatment modalities are used to treat Hodgkin lymphoma, surgery has a limited role regardless of stage. Surgery is important for an accurate diagnosis via excisional biopsy, and on certain other occasions, such as placement of a central line. The following sections will review treatment of early-stage favorable disease, early-stage unfavorable disease, advanced-stage disease, and salvage therapy.

Chemotherapy Regimens

Before the 1960s, the outcome for patients with Hodgkin lymphoma was dismal. Treatment with single-agent therapies or broad radiation fields caused excessive toxicities and few durable responses with advanced disease. The mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) regimen was introduced in the early 1960s and was the initial combination chemotherapy regimen shown to cure advanced Hodgkin lymphoma (Table 155-4). This was a tremendous advance in oncology at that time. MOPP chemotherapy was a mainstay of treatment for patients with stages III and IV advanced Hodgkin lymphoma for many years. However, investigators later learned that MOPP is associated with high rates of sterility and secondary malignancies. The young cohort of Hodgkin survivors would live long enough to endure these consequences. The research focus was then shifted to maintain the high cure rates obtained with MOPP while decreasing the long-term toxicities.

TABLE 155-4

Combination Chemotherapy Regimens for Hodgkin Lymphoma

Drug	Dosage (mg/m^2)	Route	Days
MOPP			
Mechlorethamine	6	IV	1, 8
Vincristine	1.4	IV	1, 8
Procarbazine	100	Oral	1-14
Prednisone	40	Oral	1-14
Repeat every 21 days			

ABVD			
Doxorubicin (Adriamycin®)	25	IV	1, 15
Bleomycin	10	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
Repeat every 28 days			
MOPP/ABVD			
Alternating months of MOPP and ABVD			
MOPP/ABV hybrid			
Mechlorethamine	6	IV	1
Vincristine	1.4	IV	1
Procarbazine	100	Oral	1-7
Prednisone	40	Oral	1-14
Doxorubicin	35	IV	8
Bleomycin	10	IV	8
Vinblastine	6	IV	8
Repeat every 28 days			
Stanford V			
Doxorubicin	25	IV	Weeks 1, 3, 5, 7, 9, 11
Vinblastine	6	IV	Weeks 1, 3, 5, 7, 9, 11
Mechlorethamine	6	IV	Weeks 1, 5, 9
Etoposide	60	IV	Weeks 3, 7, 11
Vincristine	1.4[a]	IV	Weeks 2, 4, 6, 8, 10, 12
Bleomycin	5	IV	Weeks 2, 4, 6, 8
Prednisone	40	Oral	Every other day for 12 weeks; begin tapering at week 10
One course (12 weeks)			

BEACOPP (standard-dose)			
Bleomycin	10	IV	8
Etoposide	100	IV	1-3
Adriamycin (doxorubicin)	25	IV	1
Cyclophosphamide	650	IV	1
Oncovin® (vincristine)	1.4[a]	IV	8
Procarbazine	100	Oral	1-7
Prednisone	40	Oral	1-14
Repeat every 21 days			
BEACOPP (escalated-dose)			
Bleomycin	10	IV	8
Etoposide	200	IV	1-3
Adriamycin (doxorubicin)	35	IV	1
Cyclophosphamide	1250	IV	1
Oncovin® (vincristine)	1.4[a]	IV	8
Procarbazine	100	Oral	1-7
Prednisone	40	Oral	1-14
Granulocyte colony-stimulating factor		Subcutaneously	8+
Repeat every 21 days			
A-AVD			
Adcetris® (brentuximab vedotin)	1.2 mg/kg	IV	1,15
Doxorubicin	25	IV	1,15
Vinblastine	6	IV	1,15
Dacarbazine	375	IV	1,15

[a]Vincristine dose capped at 2 mg.

The development of ABVD by Bonadonna et al. at the Milan Cancer Institute about a decade later represents the next important step in the evolution of therapy for Hodgkin lymphoma (see Table 155-4).[10] ABVD was initially shown to be effective in treating MOPP failures and was later compared directly to MOPP in advanced disease, where it produced an 82% complete response rate, as compared to a 67% complete response rate with MOPP. ABVD improved failure-free survival, but no significant differences in 5-year overall survival were noted.[11] Because ABVD was less toxic and provided similar or better outcomes than MOPP, it eventually replaced MOPP as the standard regimen for advanced-stage Hodgkin lymphoma.

In the early 1980s, the Goldie–Coldman hypothesis proposed that chemotherapy resistance was related to spontaneous mutation rates and the development of resistant clones. To test that hypothesis, researchers designed several clinical trials to evaluate the efficacy of alternating non–cross-resistant drug combinations in patients with Hodgkin lymphoma.[12] The initial approach adopted by investigators was to alternate or combine the MOPP and ABVD regimens. When MOPP and ABVD (or doxorubicin [Adriamycin®], bleomycin, vinblastine [ABV]) are combined in a monthly cycle, it is referred to as a hybrid regimen. Besides a potential benefit in efficacy, another potential benefit of alternating or hybrid regimens is the decreased risk of long-term toxicities. In the alternating MOPP/ABVD regimen, the cumulative doses of procarbazine and mechlorethamine are reduced by 50%, and the cumulative doxorubicin dose is reduced by 50%. In the hybrid regimen, the cumulative doxorubicin dose is reduced by 33%, and the cumulative bleomycin dose is reduced by 50%.

Several clinical trials have been performed to evaluate the efficacy of alternating or hybrid MOPP/ABVD regimens. The results of these trials show that alternating and hybrid regimens are superior to MOPP but not to ABVD.[12,13] Another approach evaluated by researchers was the administration of sequential cycles of MOPP and ABVD (MOPP/ABVD). Results of an intergroup trial showed sequential MOPP and ABVD to be inferior to the MOPP/ABV hybrid regimen in terms of response and survival.[13] In another randomized comparison trial of the MOPP/ABV hybrid regimen and ABVD, the complete remission rate, failure-free survival, and overall survival were similar between the two regimens.[14] The latter trial was closed prematurely because of an increased number of treatment-related deaths and secondary malignancies in the patients who received the MOPP/ABV hybrid regimen.

More complex regimens, such as Stanford V and BEACOPP, have been evaluated as alternatives to MOPP or ABVD. Radiation therapy is an integral part of the Stanford V regimen for all patients. The Stanford V regimen generated considerable interest based on the results of phase II trials.[15] Stanford V, ABVD, and an MOPP/ABV hybrid-like regimen (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine [MOPPEBVCAD]) were then compared in a randomized trial to determine the best regimen to support a reduced radiotherapy program.[16] Five-year failure-free and progression-free survival were significantly worse for the Stanford V regimen as compared to the other two regimens. However, no significant differences in overall response rate or 5-year overall or failure-free survival were observed between Stanford V and ABVD in a published randomized trial of patients with advanced Hodgkin lymphoma (E2496).[17] Investigators have speculated that differences in the application of radiotherapy may explain the divergent results in the randomized trials. More pulmonary toxicity occurred in the ABVD group, but other toxicities occurred more frequently in the Stanford V group.

The German Hodgkin Study Group (GHSG) developed the BEACOPP regimens based on the principles of dose density, dose intensity, and mathematical modeling. BEACOPP uses similar drugs as in the cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)/ABVD regimen, but rearranges the drugs in a shorter 3-week cycle. Several different versions of BEACOPP have been developed: standard-dose BEACOPP, escalated-dose BEACOPP, and dose-dense BEACOPP (BEACOPP-14). Granulocyte colony-stimulating factor support is required for the escalated-dose BEACOPP and BEACOPP-14 regimens.

The initial evidence for these regimens focused on patients with advanced or metastatic disease, but subsequent trials have focused on the use of these regimens in early-stage disease.

1 With all stages and risk groups of Hodgkin lymphoma, it is current practice to treat with chemotherapy for 8 to 12 weeks and then obtain a restaging PET-CT.[18] This scan is assessed on a PET 5-point scale, also known as the Deauville Criteria based on visual assessment of radiolabeled glucose uptake in involved sites. Score 1 indicates no uptake and can be called a complete response or no measurable disease.[6] For all stages of Hodgkin lymphoma, further treatment is based on the restaging PET/CT results such that residual uptake at the end of chemotherapy would likely indicate the need for ISRT. If a Deauville score of 5 exists after completion of chemotherapy, then a biopsy of the involved area is indicated. With an interval PET/CT scan, every patient's treatment plan is personalized based on the response to treatment.

Classical Hodgkin Lymphoma

Hodgkin lymphoma can initially be divided into two broad classifications: classical Hodgkin lymphoma and NLPHL. Although classical Hodgkin lymphoma can be further divided into pathologic subtypes, the treatments are based on risk factors and the presence of bulky disease regardless of the subtype of classical Hodgkin lymphoma.

Treatment of Early-Stage Favorable Disease

Patients with early-stage favorable disease have stage IA or IIA disease and no adverse risk factors (B symptoms, extranodal disease, bulky disease, three or more sites of nodal involvement, or an ESR of >50 mm/hr [13.9 µm/s]). Extended-field radiation was previously considered the treatment of choice for stages IA and IIA disease. Although most patients were cured of their disease, the radiation is associated with long-term toxicities due to large radiation fields such as heart disease, pulmonary dysfunction, and secondary malignancies.[3]

Combined modality therapy (chemotherapy and radiation therapy) has replaced radiation therapy alone in patients with early-stage favorable disease. With combined modality therapy, both a shorter duration of chemotherapy and newer, more focused radiation techniques (ISRT, others) are used to decrease the long-term toxicities of both.

Clinical trials comparing radiation alone to radiation plus chemotherapy show lower relapse rates in patients treated with combined modality therapy (radiation and chemotherapy), but no change in overall survival because of the availability of effective salvage therapy. Ongoing trials focus on questions such as the optimal number of chemotherapy cycles, the volume of radiation that must be used to obtain optimal patient outcomes, and the role of PET scanning to individualize therapy. Long-term results of clinical trials also suggest that as few as two cycles of Stanford V or ABVD chemotherapy followed by IFRT is sufficient in favorable, early-stage disease patients.[19,20] Different combination chemotherapy regimens have been used in these studies and no one regimen is superior to another.

Clinical trials have also investigated the use of chemotherapy alone to treat low-risk early-stage Hodgkin lymphoma. Long-term results of clinical trials show a lower rate of disease control versus combined modality therapy. Selected patients can be treated with chemotherapy alone if they achieve a complete response following two cycles of chemotherapy, with a total treatment of four cycles of chemotherapy.

Patients with early-stage favorable disease can be treated with two cycles of ABVD alone or plus ISRT or two to four cycles of the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone), followed by a restaging PET-CT scan.[19,20] Depending on the response to the initial chemotherapy, consolidative ISRT is recommended if anything less than a complete response is achieved. With this approach, 5-year progression-free and overall survival rates of more than 90% can be achieved in early-stage favorable disease.

Treatment of Early-Stage Unfavorable Disease

Patients with early-stage disease who have certain features associated with a poor prognosis (B symptoms, extranodal disease, bulky disease, three or more sites of nodal involvement, or an ESR >50 mm/hr [13.9 µm/s]) are defined as having unfavorable disease. Different research groups or clinical trials have different definitions for unfavorable disease. Most groups consider an ESR >50 mm/hr (13.9 µm/s), presence of B symptoms, large mediastinal mass, and more than three affected nodal sites to be unfavorable risk factors. Current guidelines recommend combined modality therapy (combination chemotherapy and ISRT) to reduce the relapse rate and avoid the toxicity associated with extended-field radiation.[18]

Randomized trials show that combined modality therapy reduces the relapse rate in patients with early-stage unfavorable disease. Different chemotherapy regimens and the number of chemotherapy cycles have been compared in clinical trials. In most studies involving early-stage unfavorable disease, ABVD is the comparator arm. ABVD plus 30 Gy [3,000 rad] ISRT remains the standard of care for patients with early-stage unfavorable disease, but the Stanford V regimen plus radiation or BEACOPP for two cycles followed by ABVD for two cycles are both alternatives in select patients. The Stanford V regimen has been studied in several single arm trials[15,21] and comparative trials versus ABVD[17,22] report overall response rates in the 90% range and 5-year overall survival from 88% to 94%. All of these trials included radiation therapy as part of the treatment schema. The GHSG studied the use of a more aggressive regimen of escalated-dose BEACOPP for two cycles followed by ABVD for two cycles versus ABVD for four cycles. Both treatment arms received 30 Gy [3,000 rad] of IFRT. Patients treated with BEACOPP had longer progression-free survival but similar 5-year overall survival as compared with ABVD.[23] Stanford V and BEACOPP are associated with more toxicities than ABVD in early-stage unfavorable Hodgkin lymphoma.[17,24]

In summary, most patients with early-stage disease will be treated with two to four cycles of ABVD chemotherapy and involved-site radiation. The number of cycles initially administered is based on the classification of favorable versus unfavorable disease. Restaging with a PET-CT after 4 to 12 weeks of chemotherapy further guides the need for more chemotherapy or radiation (ISRT), but most patients with unfavorable disease will require radiation. Clinical trials have demonstrated the utility of PET scans as biomarkers to personalize therapy and minimize the amount of therapy necessary for cure.[6] Despite excellent results from treatment with ABVD and radiation, about 5% of patients do not respond to initial treatment and another 15% of patients will relapse following an initial response.

Treatment of Advanced-Stage Disease

Advanced-stage disease consists of stages III and IV disease. In some studies, stage IIB with a large mediastinal mass or extranodal disease is also considered advanced-stage disease (see Table 155-2). By definition, patients with stages III and IV disease have tumors on both sides of the diaphragm, which almost always precludes the use of radiation alone as a therapeutic modality. Intensive combination chemotherapy is the mainstay of treatment, although some patients will benefit from radiation following chemotherapy. The prognosis of advanced-stage disease is excellent with 5-year overall survival rates ranging from 56% to 90%. Most patients obtain a complete response from their initial treatment. Prognostic factors have been identified and standardized to predict an individual's prognosis, according to the IPS (see Table 155-3).[7]

Patients with advanced-stage Hodgkin lymphoma can be classified into two groups based on the number of prognostic factors present from the IPS (see Table 155-3). Advanced-stage patients with three or fewer poor prognostic factors are considered to have favorable disease and have about a 60% likelihood of being failure-free at 5 years with traditional combination chemotherapy. Advanced-stage patients with four or more poor prognostic factors are considered to have unfavorable disease and a less than 50% likelihood of being failure-free at 5 years with traditional combination chemotherapy. Cures are possible in patients with high-risk disease, but long-term disease control is a more realistic goal for most patients.

Doxorubicin (Adriamycin®), bleomycin, vinblastine, and dacarbazine (ABVD) for decades have continued to be the standard initial regimen for advanced Hodgkin lymphoma in many cancer programs. As discussed in the section "Chemotherapy Regimens," many international randomized large trials have demonstrated ABVD's sustained positive outcomes and lower toxicity profile as compared to other regimens.

The BEACOPP regimens were designed to provide a more aggressive treatment for advanced disease. Several randomized trials have compared BEACOPP to other regimens.[3,25] The GHSG conducted a large randomized comparison of COPP/ABVD (alternating), BEACOPP, or an escalated-dose BEACOPP regimen (HD9 trial).[25] Escalated-dose BEACOPP was the most active regimen in this study, with 10-year freedom from treatment failure at 82% and overall survival at 86%, but this regimen was also associated with more toxicities, including secondary leukemias, and was particularly toxic in older adults.[26] In the HD2000 study, patients with advanced Hodgkin lymphoma were randomized to receive six cycles of ABVD, four cycles of escalated-dose BEACOPP with two cycles of standard-dose BEACOPP, or a third chemotherapy regimen that is not a current standard of care.[27] BEACOPP was superior to ABVD for 5-year progression-free survival (81% vs 68%), but 5-year overall survival was not significantly different between ABVD and BEACOPP. BEACOPP may be superior to ABVD in patients with high-risk advanced Hodgkin lymphoma (IPS ≥3). Higher rates of neutropenia and severe infections were observed with BEACOPP as compared with ABVD. The HD2000 trial also demonstrated a higher risk of secondary malignancy in the BEACOPP versus ABVD arm at 10 years.[28] Finally, GHSG has conducted several trials to evaluate the optimal number and intensity of BEACOPP. The HD12 and HD15 trials are two examples of this research.[29,30] The results of these studies suggest that escalated-dose BEACOPP is superior to ABVD in the treatment of advanced Hodgkin lymphoma, but at the cost of more treatment-related toxicity.

Current treatment options for patients with advanced disease are ABVD or escalated-dose BEACOPP. BEACOPP may be considered in patients less than 60 years old with an IPS of greater than or equal to 4.[30] As with earlier stage disease, combination chemotherapy should be administered for 4 to 18 weeks, depending on the regimen, followed by a restaging PET scan. Based on the residual Deauville score, additional chemotherapy and/or radiation may be administered. The Response-Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) trial evaluated the use of AVD, ABVD and escalated-dose BEACOPP based on interim PET-CT results after two cycles of ABVD. Those patients with a favorable response on PET-CT received either 4 cycles of ABVD or AVD. There was no difference in 3-year progression-free or overall survival, but there was less pulmonary toxicity in the AVD group due to the omission of bleomycin. Those patients with an unfavorable response on interim PET-CT had treatment intensified to dose-escalated BEACOPP with a 3-year progression-free survival and overall survival of 67.5% and 87.8% respectively.[31]

Brentuximab vedotin is an antibody-drug conjugate (ADC) comprised of an anti-CD30 antibody conjugated by a protease cleavable linker to a potent

antimicrotubule agent, monomethyl auristatin E (MMAE). After the ADC binds to CD30 on the cell surface, the ADC-CD30 complex is internalized and then releases MMAE via proteolytic cleavage in the lysosomal compartment. Tubulin binding by MMAE disrupts the microtubule network, which causes apoptotic death of the cancer cells. The A-AVD regimen incorporates brentuximab vedotin instead of bleomycin into the "AVD" backbone (doxorubicin, vinblastine, and dacarbazine). In a large international phase III trial, A-AVD was compared to ABVD in patients with newly diagnosed stage III or IV Hodgkin lymphoma. Toxicities differed in the two arms, where neutropenia, neutropenic fever, and peripheral neuropathy were more common in the A-AVD arm as compared to ABVD. Grade 3 or higher pulmonary toxicity was more common in patients receiving ABVD arm as compared to A-AVD. Of the deaths that occurred in this trial, 11 of the 13 receiving ABVD were associated with pulmonary toxicities, and 7 of the 9 receiving A-AVD were associated with neutropenia. The authors concluded that A-AVD was superior to ABVD, based on the absolute difference of 4.9% in the combined risk of death, progressive disease or incomplete response. Possible candidates for the A-AVD regimen are patients with newly diagnosed disease, no preexisting neuropathy, and a contraindication to bleomycin.[32] A+AVD group has improved progression-free and overall survival compared with ABVD (6-yr overall survival, 93% vs 89%, respectively) and thus is a first-line regimen option for patients with advanced disease.[33]

3 In summary, there are several approaches to the initial treatment of stages III and IV Hodgkin lymphoma. A standard treatment of advanced-stage favorable Hodgkin lymphoma is to administer two cycles of ABVD chemotherapy followed by a restaging PET-CT. If minimal disease is found (Deauville score 1-3), four additional courses of AVD should be given (total of six cycles). If residual disease is suspected (Deauville score 4-5), a switch to escalated-BEACOPP for four cycles should be considered. Escalated-dose BEACOPP or A-AVD for six cycles should be considered for select patients with unfavorable disease. This risk-adapted approach should result in 70% to more than 90% of patients achieving a complete remission and 60% to 80% of patients being cured of their disease. No further treatment is needed for patients who achieve a complete remission (Deauville 1-2) with chemotherapy alone. Patients who achieve a partial remission (Deauville 3-5) should be considered for consolidative radiation to residual sites of disease. As with all stages and risk-groups of Hodgkin lymphoma, if a Deauville score of 5 remains after completion of initial chemotherapy, a biopsy is recommended to determine if refractory disease is present.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma has been described as more indolent in nature, and has a better prognosis as compared with classical Hodgkin lymphoma. The use of radiation alone for stages I and II NLPHL patients who choose to omit chemotherapy or who cannot tolerate chemotherapy does not adversely affect survival.[18] The disadvantage of radiation therapy alone as compared with combination chemotherapy plus radiation is the higher relapse rate. Patients who relapse after radiation alone (20%-25%) can be successfully salvaged with chemotherapy. If the decision is made to use radiation alone, ISRT is the preferred method. Patients with advanced-stage disease can be treated with combined chemotherapy and radiation therapy. Historically, MOPP and MOPP/ABVD have been used, but these regimens have fallen out of favor much like classical Hodgkin lymphoma. ABVD is frequently used in these patients due to the available evidence to support its use for classical Hodgkin lymphoma, although other regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and CVP (cyclophosphamide, vincristine, and prednisone), have been studied. No randomized clinical trials of different chemotherapy regimens have been conducted in NLPHL. NLPHL reliably expresses CD20 and therefore rituximab has demonstrated efficacy in both newly diagnosed and progressive NLPHL. Several phase II trials have reported overall response rates of 90% to 100% with single-agent rituximab.[34,35] Current NCCN guidelines recommend that patients with stage IA or IIA nonbulky disease preferentially be treated with ISRT alone. In select patients with stage IA disease that was completely resected with the excisional biopsy, observation may be an option. Patients with IB, IIB, or advanced disease should receive chemotherapy with or without rituximab and with or without ISRT.[18]

Treatment of Refractory or Relapsed Disease

4 Refractory disease is defined as disease that persists following initial therapy, including any response less than a complete response. Relapsed disease suggests tumor recurrence following attainment of a complete response. Patients who experience relapsed disease less than 12 months after the completion of therapy have a poor prognosis. The goal of second-line or salvage therapy is still cure. With the increasing use of chemotherapy with or without radiation, regardless of disease extent, the rate of primary refractory disease is decreasing. Many therapeutic options are available for treatment of refractory or relapsed disease, so each patient's treatment should be personalized. The highest survival and cure rates are reported for patients with chemosensitive disease who are medically able to undergo high-dose therapy and autologous HSCT.[36] Since most patients are initially treated with ABVD, doxorubicin should be avoided in salvage chemotherapy regimens if the cumulative dose has reached between 300 and 400 mg/m^2, particularly in those patients who have received mediastinal radiotherapy, because of the higher risk of cardiotoxicity.

The response to salvage therapy depends on the extent and site of recurrence, previous therapy, and duration of initial remission. Patients who relapse after radiation therapy alone have a good chance of being cured with combination chemotherapy, although fewer patients are being treated with radiation alone. High response rates (60%-87%) have been reported with salvage chemotherapy regimens.[2,3] Other patient groups who have a favorable prognosis following salvage therapy include patients who experience a local recurrence in a nonirradiated location and those who relapse more than 1 year after completion of their initial chemotherapy. Patients who experience late relapses can be cured with retreatment with the same chemotherapy regimen, treatment with a different, potentially non–cross-resistant regimen, or high-dose chemotherapy and autologous HSCT.

Patients who have an early relapse (<1 year after treatment) generally respond poorly to standard-dose salvage chemotherapy. High-dose chemotherapy and autologous HSCT are more effective, but also produce a higher risk of treatment-related mortality. Therefore, the choice of salvage treatment should consider the patient's tolerance for a particular set of chemotherapeutic agents and treatment approach (standard-dose chemotherapy vs high-dose chemotherapy and autologous HSCT).

High-dose therapy should be considered in patients who relapse within 12 months of initial remission and in those who are refractory to first-line chemotherapy. Although no single preparative regimen is superior to another, most regimens do not include total-body irradiation because of its potential pulmonary toxicity. Most patients are already at higher risk for pulmonary toxicity because of previous exposure to one or more of the following: bleomycin, thoracic radiation, and nitrosoureas.

Brentuximab vedotin is effective in the relapsed or refractory setting. In a pivotal multicenter phase II study of 102 patients with relapsed or refractory Hodgkin lymphoma after HSCT, 75% and 34% of patients treated with brentuximab vedotin had an objective response and complete remission, respectively.[37] End-of-study results showed that response to brentuximab was durable; patients who achieved complete remission had an overall survival rate of 64% at 5 years and 26% remained in remission with no further anti-cancer therapy after receiving brentuximab.[38] Brentuximab vedotin has also been evaluated as posttransplant consolidation therapy in a phase III trial in 329 patients undergoing autologous HSCT. All patients had a high risk of relapse, defined as disease refractory to initial therapy or relapsed disease less than 12 months from completion of initial therapy with extranodal disease. Patients randomized to receive 16 cycles of brentuximab had significantly longer median progression-free survival (42.9 vs 24.1 months) as compared with placebo.[39] Common toxicities associated with brentuximab vedotin include neuropathy, neutropenia, nausea, and fatigue.[37] Based on these results, brentuximab vedotin received FDA approval for the treatment of classical Hodgkin lymphoma after failure of autologous HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for autologous HSCT, and also for patients with classical Hodgkin lymphoma at high risk of relapse or progression as consolidation therapy after autologous HSCT.

Many single-agent and combination regimens can be used as salvage therapy. In this setting, the goal of therapy is disease control and cures are unlikely. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), ifosfamide, carboplatin, and etoposide (ICE) and ifosfamide, gemcitabine, and vinorelbine are examples of chemotherapy regimens that include drugs with different mechanisms of action and toxicity profiles than regimens used earlier in therapy. Bendamustine, lenalidomide, and everolimus have shown activity in patients with refractory or relapsed Hodgkin lymphoma.

Immune checkpoint inhibitors, specifically PD-1 (programmed death 1 pathway) inhibitors, are treatment options in refractory Hodgkin lymphoma. Promising results have been reported from phase II trials of heavily pretreated patients. One trial with single-agent nivolumab reported an objective response rate of 87%, with some complete responses; progression-free survival at 24 weeks was 86%.[40] In another phase II trial of nivolumab in 80 patients with classical Hodgkin lymphoma after failure to both HSCT and brentuximab (median of 4 previous therapies), objective responses were achieved in two-thirds of patients.[41] Pembrolizumab, another PD-1 inhibitor, has also been studied in patients with relapsed or refractory disease. In a trial of 31 heavily pretreated patients, a complete response rate of 16% and a partial remission rate of 48% were observed, and the 52-week progression-free survival rate was 46%.[42] A large phase II trial of 210 patients treated with pembrolizumab 200 mg IV every 3 weeks also reported an overall response rate of 69% and a complete response rate of 22%.[43] Based on these results, both nivolumab and pembrolizumab received FDA approval for relapsed Hodgkin lymphoma. Potentially severe graft-versus-host disease has been described in patients who received a checkpoint inhibitor following allogeneic HSCT.[44]

Long-Term Complications

A variety of acute and chronic toxicities may occur as a result of treatment for Hodgkin lymphoma. Long-term complications of radiation therapy,

chemotherapy, and combined modality therapy have become more evident as the curability and long-term survival of Hodgkin lymphoma patients have improved.[2,3,18,45] Gonadal dysfunction (including sterility and hypothyroidism), secondary malignancies, and cardiopulmonary diseases are important considerations in the treatment of this malignancy. Almost all men and up to 50% of premenopausal women treated with six cycles of regimens containing alkylating agents become sterile. This is a dose-related phenomenon. For men, even a single dose of nitrogen mustard or chlorambucil can cause sterility, so if fertility is a major concern, ABVD is the best alternative.

The risk of secondary malignancies is increased about threefold in long-term survivors of Hodgkin lymphoma. The risk of developing leukemia carries the highest increase in risk and is seen with radiotherapy, chemotherapy, and chemoradiotherapy. Solid tumors, including breast cancers, gastrointestinal cancers, and lung cancers, are also likely to develop more than 10 years after the completion of treatment. A recently published British cohort study suggested that unlike radiotherapy, which may increase the occurrence of cancer at almost all anatomic sites, chemotherapy is associated with an increased risk of leukemia, NHL, and lung cancer. However, studies that evaluate the risk of secondary malignancies (and other complications) must be interpreted cautiously because many factors probably contribute to the development of secondary malignancies. In addition, much of the long-term complication data are derived from patients who were treated with older regimens and extensive field radiotherapy, which are no longer commonly used in clinical practice. As the field of cancer survivorship continues to grow, more specific recommendations for long-term follow-up are developed. Regular mammograms and breast MRI are recommended starting 10 years following the completion of therapy or at age 40 (whichever is earlier) for females. Patients are at increased risk of lung cancer if they have a smoking history, chest irradiation, and/or alkylating agent exposure. These patients should be considered for low-dose screening chest CT. For cardiovascular monitoring, annual blood pressure monitoring and aggressive management of cardiovascular risk factors are strongly encouraged. Hypothyroidism is reported in about 50% of long-term survivors who received irradiation to this area. Thyroid function tests should be performed annually. Monitoring and follow-up should be personalized after assessing a patient's risks for long-term complications.[18]

NON-HODGKIN LYMPHOMA

The NHLs are a heterogeneous group of lymphoproliferative disorders that affect individuals from early childhood to late adulthood. Advances in molecular biology techniques and our understanding of the human immune system have led to major progress in understanding the pathogenesis and treatment of lymphomas. NHLs are classified into distinct clinical entities defined by a combination of morphology, immunophenotype, genetic features, and clinical features. These differences influence the natural history, approach, and response to treatment. The use of extensive combination chemotherapeutic regimens shows dramatic improvement in survival and cure in patients with a disease that was once considered incurable. The 5-year survival rate for patients with NHL has increased from 48% to 73% over the past 30 years, and the mortality rate actually *declined* from 1997 to 2015.[1] Further improvement in survival is anticipated with the continued expansion of our therapeutic armamentarium, including high-dose chemotherapy and targeted therapy.[1]

Epidemiology and Etiology

NHL is the fifth most common cause of newly diagnosed cancer in the United States and accounts for about 4% of all cancers. An estimated 80,550 new cases were diagnosed in 2023, and 20,180 people will die from NHL during this same period.[4] Although the average age of patients at the time of diagnosis is about 67 years, NHL can occur at any age. The incidence rate generally increases with age and is higher in men than in women and in white patients than in black patients.[4] The age-adjusted incidence rate of NHL increased by more than 80% in the United States since the early 1970s, from about 11 cases per 100,000 in 1975 to about 20 cases per 100,000 in 2011 and 2012.[1] The incidence of NHL increased by 3% to 4% from 1975 to 1991, but has finally begun to decline since reaching its peak in 1994. The increased incidence of NHL over the past three decades is second only to melanoma and has been referred to as an epidemic of NHL. Although the increase has been noted particularly among older adults and patients with acquired immune deficiency syndrome (AIDS), much of it cannot be explained by known risk factors.

The etiology of NHL is unknown, although several genetic diseases, environmental agents, and infectious agents are associated with the development of NHL. An increased incidence of NHL is seen in many congenital and acquired immunodeficiency states, supporting the role of immune dysregulation in the etiology of NHL. Patients with congenital immunodeficiency disorders such as Wiskott–Aldrich's syndrome and ataxia telangiectasia, acquired immunodeficiency disorders such as AIDS, and those receiving chronic pharmacologic immunosuppression in the setting of solid-organ transplantation are predisposed to the development of NHL. Autoimmune diseases (Hashimoto's thyroiditis and Sjögren's syndrome) cause chronic inflammation in the mucosa-associated lymphoid tissue (MALT), which predisposes patients to subsequent lymphoid malignancies. Other

autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, are also associated with the development of NHL, but the use of immunosuppressive agents in these diseases makes the pathologic cause less clear.

Certain infections are associated with the development of lymphoma. EBV was discovered in cell lines from tumors of patients with African (endemic) Burkitt lymphoma, and EBV DNA is associated with nearly all cases of endemic Burkitt lymphoma. However, EBV is associated with sporadic Burkitt lymphoma in 15% to 85% of cases. EBV is also associated with posttransplant lymphoproliferative disorders and some lymphomas in patients with AIDS or congenital immunodeficiencies. Extranodal NK-T cell lymphoma is also strongly associated with EBV infection. The nasal-type extranodal NK-T cell lymphoma is more common in East Asia, and less common in Central and South America than in other regions. The human T-cell lymphotropic virus type 1 was the first human retrovirus associated with malignancy. Infection with human T-cell lymphotropic virus type 1, especially in early childhood, is strongly associated with an aggressive form of T-cell lymphoma, known as adult T-cell leukemia/lymphoma. Human T-cell lymphotropic virus type 1 is endemic in parts of southern Japan, Africa, South America, and the Caribbean. In endemic areas, more than 50% of all NHL cases are adult T-cell leukemia/lymphoma. A third virus associated with NHL is human herpesvirus 8 (also referred to as Kaposi sarcoma–associated herpesvirus [KSHV]). This virus was originally isolated from Kaposi sarcoma lesions in AIDS patients. Gastric infection with *Helicobacter pylori*, a gram-negative bacteria that leads to chronic gastritis, is associated with gastric MALT lymphomas. Finally, hepatitis C virus has been associated with splenic and nodal marginal zone lymphomas.

Several physical agents are also associated with the development of NHL. Exposure to herbicides, particularly phenoxyl herbicides, is associated with the development of NHL. These observations may explain why certain occupations, such as farmers, forestry workers, and agricultural workers, are associated with a higher risk of NHL. Exposure to lawn-care pesticides is also increasing in the general population. A higher risk of NHL is also associated with exposure to other chemical solvents and dyes, exposure to radiation from nuclear explosions, and high intake of meats and dietary fats. Smoking or alcohol consumption is not strongly associated with an increased risk of NHL.

Molecular Abnormalities

Chromosomal translocations are a hallmark of many lymphoid malignancies.[46] The presence of these specific translocations can be helpful in the diagnosis and classification of lymphoid malignancies. The mechanisms leading to the translocations are unknown, but they usually involve the antigen receptor loci. In contrast to most myeloid and some lymphoid leukemias, NHLs usually place a structurally intact cellular proto-oncogene under the regulatory influence of highly expressed immunoglobulin or T-cell receptor genes, leading to effects on cell growth, cellular differentiation, or apoptosis. The most common chromosomal translocations involve t(8;14), t(14;18), and t(11;14); each translocation involves the immunoglobulin heavy-chain gene locus on chromosome 14 at 14q32. The translocation t(8;14) that involves c-*MYC*, a well-characterized oncogene associated with malignancy, is implicated in nearly all cases of Burkitt lymphoma. The translocation t(14;18) that involves *BCL*-2, one of several putative B-cell lymphoma-associated oncogenes, is found in about 90% of cases of follicular B-cell lymphomas. The translocation t(11;14) that involves *BCL*-1 is found in about 70% of patients with mantle cell lymphoma (MCL). Another putative B-cell lymphoma-associated oncogene, *BCL*-6, is found in about one-third of diffuse large B-cell lymphomas (DLBCLs).

Although mutations in the *p53* tumor suppressor gene are found in many human neoplasms, such mutations have not been consistently found in patients with lymphoma, which suggests that it may occur late in malignant evolution. Because of their role in the pathogenesis of lymphoma, oncogenes are attractive molecular targets for new and novel therapies.

Pathology and Classification

NHLs are neoplasms derived from the monoclonal proliferation of malignant B or T lymphocytes and their precursors. About 85% to 90% of NHLs in the United States are of B-cell origin. Proliferation of malignant cells replaces the normal cells and architecture of lymph nodes or bone marrow with a relatively uniform population of lymphoid cells. The current classification schemes characterize the NHLs according to the cell of origin (B cell vs T cell), clinical features, and morphologic features. Additional immunohistochemical markers, cytogenetic features, and genotypic characteristics may further classify NHL into subtypes.

5 The 2016 WHO classification categorizes lymphoid malignancies into two major categories: B-cell lymphomas and T-cell (and natural killer cell) lymphomas (see Table 155-1).[47] B-cell lymphomas represent about 85% to 90% of all NHLs. Lymphomas within each category can be divided into malignancies of precursor or mature cells. Hodgkin lymphoma and multiple myeloma are recognized as mature B-cell neoplasms. The WHO classification uses the term *grade* to refer to histologic parameters such as cell and nuclear size, density of chromatin, and proliferation fraction, and

the term *aggressiveness* to denote clinical behavior of a tumor. This classification scheme includes both lymphomas and lymphoid leukemias, because there is no distinction between the solid and circulating forms of these diseases. The WHO classification includes several previously unrecognized types of lymphomas, and new entities not specifically recognized in the Working Formulation account for about 20% to 25% of the cases.

The WHO classification has broad clinical implications. The WHO Clinical Advisory Committee has agreed that clinical groupings of lymphoid neoplasms into prognostic categories are neither necessary nor desirable because such arbitrary groupings are of no practical value and may be misleading.[48]

Clinical Presentation

CLINICAL PRESENTATION: Non-Hodgkin Lymphoma

General

- Patients with NHL present with a wide variety of symptoms, depending on the site of involvement and whether tumor involvement is nodal or extranodal.

Symptoms

- About 40% of patients present with fever, night sweats, and weight loss (ie, B symptoms).
- Fatigue, malaise, and pruritus.

Signs

- More than two-thirds of patients present with peripheral lymphadenopathy.

Laboratory Tests

- A complete blood count, tests of renal and liver function, and serum electrolytes should be obtained.
- Serum β_2-microglobulin and LDH levels may be useful as prognostic factors and for monitoring response to therapy.

Other Diagnostic Tests

- Varies depending on the sites of involvement.

6 Patients with NHL present with a wide variety of symptoms, depending on the site of involvement and whether tumor involvement is nodal or extranodal. Sites of involvement and dissemination of the malignant cells can sometimes be predicted based on the cell of origin and the tendency of tumors to frequently disseminate to areas where the normal counterparts of the lymphoma cells are located. For example, B-cell lymphomas involve areas of the lymphoid system normally populated by B-lymphocytes such as lymph nodes, spleen, and bone marrow. T-cell lymphomas commonly disseminate to various extranodal sites such as the skin and lungs.[46]

Most patients present with peripheral lymphadenopathy. The lymphadenopathy may be either localized or generalized, and the involved nodes are often painless, rubbery, and discrete, and usually located in the cervical and supraclavicular regions as in Hodgkin lymphoma (see Fig. 155-1). Rapid and progressive lymphadenopathy is more characteristic of aggressive lymphomas. Waxing and waning of lymph nodes, including their complete disappearance and reappearance, is more characteristic of indolent lymphomas. Massive lymphadenopathy can sometimes lead to organ dysfunction. For example, patients with NHL may present with acute renal failure from retroperitoneal adenopathy causing ureteral obstruction or from metabolic abnormalities such as hyperuricemia with uric acid nephropathy.

About 40% of patients with NHL present with fever (temperature >38°C [100.4°F]), weight loss (unexplained weight loss of 10% of body weight over the past 6 months), or night sweats (drenching night sweats). If one or more of these symptoms are present, the patient is noted to have B symptoms, and a

B is added to the stage of disease (discussed in the section "Diagnosis, Staging, and Prognostic Factors" under Hodgkin Lymphoma earlier in this chapter). B symptoms are more commonly observed in patients with aggressive NHLs.

Patients with Hodgkin lymphoma rarely present with extranodal (ie, extralymphatic) disease, but 10% to 35% of patients with NHL have primary extranodal disease at the time of diagnosis. The frequency of extranodal presentation varies dramatically among different subtypes. The most common extranodal sites are the gastrointestinal tract followed by the skin. The liver or spleen may be enlarged in patients with generalized adenopathy. Patients with mesenteric or gastrointestinal involvement may present with signs and symptoms of nausea, vomiting, obstruction, abdominal pain, a palpable abdominal mass, or gastrointestinal bleeding. Patients with bone marrow involvement may have symptoms related to anemia, neutropenia, or thrombocytopenia. Other sites of extranodal disease include the testes and bone. The incidence of solitary brain lymphoma is increasing, especially in patients with AIDS.

Diagnosis, Staging, and Prognostic Factors

As with Hodgkin lymphoma, the diagnosis of NHL must be established by pathologic review of tissue obtained by biopsy.[46,49,50] The preferred procedure is an excisional biopsy, where the entire involved lymph node is removed for review by an experienced hematopathologist. This procedure should be done carefully to prevent distortional artifact of the architecture, which could lead to an inaccurate diagnosis. Needle biopsy of the node can sometimes provide adequate tissue for pathologic diagnosis if an excisional biopsy cannot be performed. When adenopathy is not present, diagnosis may be established by biopsy of cutaneous lesions, bone marrow biopsy and aspiration in patients with unexplained myelosuppression, liver biopsy in patients with hepatomegaly or elevated liver function tests, or biopsy of involved extranodal organs such as bone, Waldeyer's ring, lung, and testis.

After the diagnosis is established, further workup is required to determine the extent of involvement.[46,49,50] Clinical staging always begins with a thorough history and physical examination. Patients should be questioned about the presence or absence and extent of fever, night sweats, and weight loss. A detailed history of lymphadenopathy should also be obtained, including when and where the lymph nodes were first noted, and their rate of growth. A complete physical examination is performed to assess the extent of disease involvement, with special attention given to all nodal areas (see Fig. 155-1). All patients should have a complete blood count, serum chemistries including liver and renal profiles. Lumbar puncture to evaluate the cerebrospinal fluid is recommended in patients who have histologic types of lymphoma that often spread to the CNS.

Imaging studies are important in the staging workup. In the most recent recommendations, PET-CT is the gold standard for assessment of essentially all lymphoma histologies, except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there is a suspicion of aggressive transformation.[50] The total metabolic tumor volume at diagnosis may play a prognostic role.[51] Magnetic resonance imaging is of limited usefulness in the staging of NHL. Gallium scans are sometimes used as part of the staging workup. Other tests, such as liver-spleen scan, bone scan, upper gastrointestinal series, and IV pyelogram, are sometimes useful in patients with organ symptomatology or serum chemistry abnormalities.

The likelihood of bone marrow involvement varies among the different histologic types of lymphoma (Table 155-6). In the NCCN guidelines, bone marrow biopsy with or without aspirate is included in the essential workup for all lymphomas. Although PET-CT scans are as sensitive as bone marrow biopsy in the identification of bone marrow involvement in certain subtypes of NHL including DLBCL, bone marrow biopsy remains preferable for identifying bone marrow involvement in indolent lymphomas such as follicular lymphoma.

The Ann Arbor staging classification developed for the clinical staging of Hodgkin lymphoma is also used to stage patients with NHL (see Table 155-2). After completion of the staging workup, most patients will be found to have advanced disease (stages III and IV). The frequency of localized disease at the time of diagnosis varies depending on the histologic type of lymphoma (see Table 155-5). Stage is a more important prognostic factor in Hodgkin lymphoma than in NHL.

TABLE 155-5

Clinical Characteristics of Patients with Common Types of Non-Hodgkin Lymphomas

Disease	Median Age (Years)	Frequency in Children	% Male	Stage I/II vs III/IV (%)	B Symptoms (%)	BM Involvement (%)	GI Tract Involvement (%)	5 Year Survival (%)
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	65	Rare	53	9 vs 91	33	72	3	51
Mantle cell lymphoma	63	Rare	74	20 vs 80	28	64	9	27
Extranodal marginal zone B-cell lymphoma of MALT type	60	Rare	48	67 vs 33	19	14	50	74
Follicular lymphoma	59	Rare	42	33 vs 67	28	42	4	72
Diffuse large B-cell lymphoma	64	≈25% of childhood NHL	55	54 vs 46	33	16	18	46
Burkitt lymphoma	31	≈30% of childhood NHL	89	62 vs 38	22	33	11	45
Precursor T-cell lymphoblastic lymphoma	28	≈40% of childhood NHL	64	11 vs 89	21	50	4	26
Anaplastic large T-/null cell lymphoma	34	Common	69	51 vs 49	53	13	9	77
Peripheral T-cell non-Hodgkin lymphoma	61	≈5% of childhood NHL	55	20 vs 80	50	36	15	25

BM, bone marrow; GI, gastrointestinal; MALT, mucosa-associated lymphoid tissue; NHL, non-Hodgkin lymphoma.

Reproduced with permission from Longo DL. Malignancies of lymphoid cells. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 19th ed. New York, NY: McGraw-Hill; 2015.

7 The Ann Arbor system emphasizes the distribution of nodal disease sites because Hodgkin lymphoma usually spreads through contiguous lymph nodes and does not involve extranodal sites. But NHL is a disease with tremendous heterogeneity that does not spread through contiguous lymph nodes and often involves extranodal sites. As a result of these clinical differences between Hodgkin lymphoma and NHL, Ann Arbor stage correlates poorly with prognosis.

8 This lack of accuracy with the Ann Arbor staging system in NHL has led to several international projects to develop prognostic models for the most common types of NHLs—DLBCLs and follicular lymphomas. The International Non-Hodgkin Lymphoma Prognostic Factors Project was based on more

than 2,000 patients with diffuse aggressive lymphomas treated with an anthracycline-containing combination chemotherapy regimen in the United States, Europe, and Canada.[52] The Project identified five risk factors that correlated with low complete response rate to chemotherapy and poor survival, and a subgroup analysis found three specific risk factors correlated with low complete response rate to chemotherapy and poor survival in patients 60 years old and above (Table 155-6). It is unclear whether the effect of serum LDH level is related to a tumor or a host event. LDH likely measures cellular catabolism (the enzyme is released from injured cells) or the product of tumor burden and proliferation. Because each of the factors has about the same impact (eg, relative risk) on prognosis, the number of adverse risk factors is summed to provide the IPI. Patients could therefore have a score of 0 to 5. For patients older than or equal to 60 years, a simplified IPI score can be determined based on Ann Arbor stage, serum LDH level, and performance status.

TABLE 155-6

Risk Factors According to the International Non-Hodgkin Lymphoma Prognostic Factors Project

All Patients	Patients ≤60 Years of Age
Age >60 years	Abnormal LDH level
Abnormal LDH level	Performance status ≥2
Performance status ≥2	Ann Arbor stage III or IV
Ann Arbor stage III or IV	
Extranodal involvement ≥2 sites	

LDH, lactic dehydrogenase.

Data from Reference 52.

It is important to periodically reevaluate prognostic factors as prognosis improves as a result of more effective therapy. The IPI was based on patients treated from 1982 to 1987 with anthracycline-based combination chemotherapy; none of the patients received rituximab. Therefore, an enhanced IPI (NCCN-IPI) was developed to stratify newly diagnosed DLBCL patients based on their clinical features (age, normalized LDH, sites of involvement, Ann Arbor, and ECOG performance status) in the rituximab era.[53] Through an independent validation, the NCCN-IPI was shown to discriminate patients in the low- and high-risk subgroups better than the IPI.

Although the IPI is often used to predict prognosis in patients with other NHL subtypes, the IPI has several shortcomings when applied to patients with indolent lymphomas. Because only patients with diffuse aggressive lymphomas were used to develop the IPI system, some important prognostic factors may have been missed. Furthermore, the IPI system has limited discriminating power in follicular lymphoma because only about 10% of patients are categorized as high-risk in the IPI system. To address these concerns, an international cooperative study was designed to develop a prognostic model similar to the IPI in patients with follicular lymphoma. The results of that study, which was based on more than 4,000 patients with follicular lymphoma diagnosed between 1985 and 1992, identified five factors that correlated with poor survival (Table 155-8).[54] Analogous to the IPI, the number of adverse risk factors is summed to provide the Follicular Lymphoma International Prognostic Index (FLIPI). FLIPI had higher discriminating power among groups as compared with the IPI system. Table 155-8 shows the number of risk factors stratified with FLIPI. The survival data from FLIPI, however, may not reflect current treatment results because none of the patients in the cohort used to derive the FLIPI were treated with rituximab. In an updated prognostic model (FLIPI-2) derived from patients with newly diagnosed follicular lymphoma treated with rituximab-containing chemoimmunotherapy regimens, age older than 60 years, low hemoglobin level (<12 g/dL [120 g/L; 7.45 mmol/L]), longest diameter of the largest lymph node more than 6 cm, abnormal β_2-microglobulin levels and bone marrow involvement were identified as adverse risk factors. FLIPI-2 was highly predictive of treatment outcomes and separated patients into three distinct risk groups: low-risk (0 factors), intermediate-risk (1 or 2 factors), and high-risk (≥3 factors). Three-year progression-free survival was 91%, 69%, and 51%, and overall survival was 99%, 96%, and 84% in low-, intermediate-, and high-risk patients, respectively.[55]

Although IPI and FLIPI are clinically useful tools to estimate prognosis, the factors used to calculate these scores probably represent clinical surrogates for the biologic heterogeneity among NHLs and many researchers are interested in determining the prognostic importance of certain phenotypic and molecular characteristics of NHLs. For example, molecular markers of apoptosis, cell-cycle regulation, cell lineage, and cell proliferation are being evaluated as potential prognostic factors.[56]

Gene expression profiling with microarrays may also correlate with survival. Using gene expression profiling, investigators identified at least two molecularly distinct types of DLBCLs based on gene expression patterns indicative of different stages of B-cell differentiation: germinal center B-cell–like (GCB) and activated B-cell–like (ABC), with 10% to 15% being unclassifiable.[56,57] The GCB subtype of DLBCL probably arises from normal germinal center B-cells while the ABC subtype may arise from postgerminal center B-cells. Many oncogenic pathways are different for the GCB and ABC subtypes, and these differences may lead to the development of targeted therapies for each subtype.[56] Patients with the germinal center B-cell profile had significantly better overall survival independent of IPI score after treatment with cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine (Oncovin®), prednisone (CHOP), or CHOP-like chemotherapy. In a published study of patients with DLBCL treated with either CHOP or rituximab and CHOP (R-CHOP), Lenz et al. identified several gene expressions signatures that predicted survival in both CHOP and R-CHOP cohorts: GCB, stromal-1, and stromal-2.[58] The GCB and stromal-1 signatures were associated with a favorable prognosis while the stromal-2 signature was associated with an unfavorable prognosis. The stromal-1 signature reflects extracellular matrix deposition and histiocytic infiltration, whereas the stromal-2 signature reflects tumor blood vessel density. It is speculated that DLBCLs that express the stromal-2 signature may respond to antiangiogenic agents.

Another important but rare molecular subtype is double-hit NHL, which is now classified by WHO as high-grade B cell lymphoma with MYC gene arrangement and BCL2 or BCL6 translocation. If all three are rearranged, it is referred to as triple-hit NHL. Patients with double-hit or triple-hit NHL have a poor prognosis, with a median overall survival that is 4 to 6 months even with highly aggressive chemotherapy.[59] Some lymphoma experts suggest that patients with double-hit NHL should be treated with more dose-intensive regimens.[56] Besides double-hit NHL, a more common molecular subtype is double-expressor NHL, accounting for 20% to 30% of DLBCL cases. Unlike double-hit NHL, patients with double-expressor lymphoma co-express MYC and BCL2 proteins without underlying chromosomal rearrangements. Double-expressor NHL is associated with a worse prognosis than other DLBCLs, but it has slightly better outcomes than double-hit NHLs. More intensive treatment regimens are also being evaluated in patients with double-expressor NHL.[60]

Two molecularly distinct profiles of follicular lymphoma have been identified. The first includes genes encoding for T-cell markers and genes highly expressed in macrophages, and the second includes genes that are preferentially expressed in macrophages, dendritic cells, or both.[61] Patients with the first molecular signature have a more favorable outcome than those with the second signature. These results suggest that molecular classification of NHL based on gene expression may allow the identification of clinically significant subtypes.

Treatment: Non-Hodgkin Lymphoma

Desired Outcomes

The primary goals in the treatment of NHL are to relieve symptoms, cure the patient of the disease whenever possible, and minimize the risk of serious toxicities. The treatment strategy depends on many factors, including the patient's age, concomitant disease, disease type, stage of disease, site of disease, and patient preference.

General Approach

Historically, the clinical behavior and degree of aggressiveness are used to describe NHLs. Indolent lymphomas, which make up about 25% to 40% of all NHLs, are characterized by their slow-growth behavior. Patients with indolent lymphoma usually have a relatively long survival (measured in years), with or without aggressive chemotherapy. Although these lymphomas respond to a wide range of therapeutic approaches, there is no convincing evidence of a survival plateau, which indicates that patients are rarely cured of their disease. In contrast, aggressive lymphomas, which make up about 60% to 75% of all NHLs, are characterized by rapid growth rate and short survival (measured in weeks to months) if appropriate therapy is not initiated. Despite their more aggressive nature, many patients with aggressive lymphomas who respond to chemotherapy can experience prolonged disease-free survival and some are cured of their disease. Therefore, the terminology for the NHLs represents a paradox, where "indolent" is bad and "aggressive" is good in terms of the likelihood of cure.

Therapeutic approaches to NHL include radiation therapy, chemotherapy, and biologic or targeted agents. The role of radiation therapy in the treatment of NHL differs from its role in the treatment of Hodgkin lymphoma. Although the disease responds to radiation therapy, only a small percentage of patients with NHL present with truly localized disease that can be treated with local or regional radiation therapy. Radiation therapy is used more commonly in advanced disease, primarily as a palliative measure to control local bulky disease.

Effective chemotherapy for NHL ranges from single-agent therapy in indolent lymphomas to aggressive, complex chemotherapy regimens in aggressive lymphomas. The most active agents used in the treatment of NHL include the alkylating agents (eg, cyclophosphamide, chlorambucil), bleomycin, doxorubicin, purine analogs, etoposide, methotrexate, vincristine, and corticosteroids (eg, prednisone, dexamethasone). The most aggressive chemotherapy approaches are dose-dense chemotherapy or high-dose chemotherapy followed by autologous or allogeneic HSCT.

B-cell lymphomas have served as a model for immunotherapy with monoclonal antibodies for more than 20 years, beginning with the successful use of custom-made monoclonal antibodies targeted against the idiotype present on the patient's cancer cells.[62] These encouraging results lead to the development of monoclonal antibodies against a more generic target, a molecule on the surface of B cells that would be present on tumor cells. One potential target, the CD20 molecule, is present only on cells in the B-lymphocyte lineage. It is expressed on the surface of both normal and malignant B cells, but not on other normal tissues. Rituximab (Rituxan®) is a chimeric monoclonal antibody directed at the CD20 molecule. Its antitumor activity is mediated through complement-dependent cytotoxicity, antibody-dependent cytotoxicity, and induction of apoptosis.[62] With the availability of monoclonal antibodies and radioimmunoconjugates for the therapy of lymphoma, nearly all patients with NHL will receive one or more biologic agents during the course of their disease.

Objective response to therapy for NHL should be defined according to the Lugano classification. The Lugano classification was established at the 12th International Conference on Malignant Lymphoma 2013. The revised guidelines describe criteria for response (eg, complete response, partial response, and stable disease) and emphasize the role of PET-CT and CT in the assessment of response in lymphoma treatment. PET-CT is recommended in FDG-avid histologies such as Hodgkin lymphoma, DLBCL, and follicular lymphoma while CT is advised for other lymphomas with low or variable FDG-avidity.[50]

Appropriate therapy for NHL depends on the patient's age, histologic type, stage of disease, site of disease, presence of adverse prognostic factors (as measured by IPI or FLIPI score), and patient preferences. In general, treatment of lymphoma can be divided into limited disease and advanced disease. Limited disease includes those patients with localized disease (Ann Arbor stages I and II). Advanced disease is defined as all Ann Arbor stage III or IV patients, and also frequently includes Ann Arbor stage II patients with poor prognostic features (see Tables 155-6 and 155-7).[52,54]

TABLE 155-7

Risk Factors According to the Follicular Lymphoma International Prognostic Index

All Patients
Age >60 years
Ann Arbor stage III or IV
Number of nodal sites ≥5
Abnormal lactate dehydrogenase level
Hemoglobin <12 g/dL (120 g/L; 7.45 mmol/L)

Risk Group (% of Patients)	Number of Risk Factors
Low (36)	0-1
Intermediate (37)	2
High (27)	≥3

The following section discusses the clinical characteristics and therapy of the most common disease entities.

Follicular Lymphomas

The combined group of follicular lymphomas makes up the second most common histologic type of NHL in the United States, comprising about 20% to 25% of all new NHLs diagnosed in western countries.[61] The WHO classification includes criteria for grading follicular lymphoma based on the number of centroblasts per high-power field: grade 1 to 2 (0-15 centroblasts/high-power field) and grade 3 (>15 centroblasts/high-power field).[5] The clinical behavior and treatment outcome of grades 1 and 2 follicular lymphoma are similar, and they are usually treated as indolent lymphomas. The current WHO classification subdivides grade 3 follicular lymphoma into grades 3A and 3B. The WHO recommends that grade 3A follicular lymphoma should be treated in the same way as low-grade follicular lymphoma, whereas grade 3B should be treated in the same way as an aggressive lymphoma.

Follicular lymphomas tend to occur in older adults, with a slight female predominance (see Table 155-5). Most patients have advanced disease at diagnosis, but about 25% to 33% of patients have localized disease (clinical stage I or II) at diagnosis.[63] Extranodal disease, bulky disease, and B symptoms are uncommon features at diagnosis. Most patients with follicular lymphoma have chromosomal translocation t(14;18) at the time of diagnosis.

The clinical course is generally indolent, with median survivals of 8 to 10 years. But the natural history of follicular lymphoma can be unpredictable. Spontaneous regression of objective disease has been noted in as many as 20% to 30% of patients. There is also a high conversion rate of follicular lymphoma to a more aggressive histology over time that steadily increases after diagnosis and reaches about 30% at 10 years.[64] At autopsy, most patients with follicular lymphoma have some evidence of DLBCL. Patients with transformed indolent lymphoma should be treated in the same way as patients with an aggressive lymphoma.

Most patients have dramatic responses to initial therapy, and their disease course is characterized by multiple relapses, with responses to salvage therapy becoming progressively shorter after every relapse, eventually leading to death from disease-related causes. This pattern of constant relapses

over time without evidence of a survival plateau and the failure of randomized controlled trials to show a survival benefit with aggressive chemotherapy led to the conclusion that therapy does not prolong overall survival or cure patients of their disease. However, the use of biologic agents, particularly rituximab, has changed the natural history of follicular lymphoma. In a study of patients enrolled in Southwest Oncology Group (SWOG) trials over more than 20 years, patients treated with CHOP and a monoclonal antibody had a significantly longer 4-year overall survival than those treated with CHOP alone (91% vs 69%).[65] With advances in therapeutics, the life expectancy of patients with follicular lymphoma has correspondingly increased. However, lymphoma is still the leading cause of death among patients diagnosed with follicular lymphoma in the rituximab era, especially among those patients experiencing disease transformation.[66]

Certain subsets of patients with follicular lymphoma have a much better or worse prognosis. The natural history of follicular large cell lymphoma (ie, grade 3 follicular lymphoma) is similar to that of other aggressive lymphomas and that treatment with intensive combination chemotherapy regimens may result in long-term disease-free survival, including a possible plateau in the survival curve.[67] The recent development of the FLIPI prognostic model should help clinicians to identify patients in different prognostic groups based on disease characteristics at the time of diagnosis.[54] Patients who are predicted to have a poor prognosis (ie, high-risk) could then be offered aggressive or experimental therapy, while those who are predicted to have a good prognosis (ie, low-risk) would be treated with standard therapy, avoiding unnecessary toxicity.

Treatment of Localized Disease (Stages I and II)

Radiation therapy is the standard treatment for early-stage follicular lymphoma. Involved-field, extended-field, and total nodal irradiation have been used. Carefully staged patients with either stage I or contiguous stage II disease treated with radiation therapy alone can achieve disease-free survival rates of 40% to 50% and overall survival rates of 60% to 70% at 10 years.[67] Late relapses are uncommon; only 10% of patients who reached 10 years without relapse subsequently experienced a recurrence.

Chemotherapy is not usually given in most patients with localized follicular lymphoma, but it may be helpful in some patients with high-risk stage II disease (eg, multiple sites of involvement or bulky disease).[68]

10 About 40% to 60% of patients with clinical stage I or II follicular lymphoma are cured of their disease with radiation therapy alone.[49] Most centers use radiation at a dose of 30 to 40 Gy (3,000-4,000 rad) to either involved (ie, local) or regional fields, which would consist of irradiation to the involved nodal region plus one additional uninvolved region on each side of the involved nodes. Extended-field irradiation is not usually used because of the absence of a survival benefit and possible increased risk of secondary malignancies. In addition, previous use of extended-field irradiation compromises the ability of that patient to receive subsequent chemotherapy. The current NCCN guideline states that locoregional radiation therapy is preferred for most patients with early-stage follicular lymphoma.[49] Anti-CD20 antibodies, in combination with chemotherapy, are also listed as an option.

Treatment of Advanced Disease (Stages II Bulky, III, and IV)

The management of stages II Bulky, III, and IV indolent lymphomas remains controversial because until recently, no therapeutic approaches had been shown to prolong overall survival despite the high complete remission rates to initial therapy. More than 80% of patients with stage III or IV follicular lymphoma are alive at 5 years, and the median survival ranges between 7 and 10 years.

Although complete remission can be achieved in 50% to 80% of patients with various treatments, the median time to relapse is usually only 18 to 36 months. About 20% of patients who have a complete response remain in remission for longer than 10 years. After relapse, patients are retreated and high remission rates can be achieved. Unfortunately, response rates and duration of response decrease with each retreatment.

Several different approaches can be used to treat follicular lymphoma. Carefully selected patients may receive no initial therapy followed by chemoimmunotherapy or single-agent anti-CD20 therapy, or radiation therapy when treatment is needed. Candidates for the conservative approach are usually older, asymptomatic, and have minimal tumor burden. Patients with symptoms, extensive extranodal involvement, bulky disease, cytopenia due to bone marrow involvement, splenomegaly and steady progression over at least 6 months, or impaired end-organ function at the time of diagnosis are not candidates for conservative treatment. Patients who respond to induction therapy may receive maintenance therapy with single-agent anti-CD20 therapy.

At the time of relapse, many of the same treatment options are available, and the following factors must be considered: age, symptomatic status of the

patient, tumor burden, rate of regrowth (based on previous assessment of active disease sites), presence or absence of characteristics suggesting transformation or biologic progression, prior therapy, degree and duration of response to prior therapy, availability of clinical trials, and patient preferences.[49]

Watch-and-Wait

Because there are no convincing data that standard treatment approaches have improved survival, some clinicians have adopted a "watch-and-wait" approach for asymptomatic patients where therapy is delayed until the patient experiences systemic symptoms or disease progression such as rapidly progressive or bulky adenopathy, anemia, thrombocytopenia, or disease in threatening sites such as the orbit or spinal cord.[68] In a randomized study of asymptomatic patients with indolent lymphomas (mostly follicular), patients who underwent watchful waiting had similar cause-specific and overall survival as compared with those who received immediate chlorambucil.[69] With a median length of follow-up of 16 years, about 17% of patients who were randomized to the watchful waiting group died of other causes without receiving chemotherapy and an additional 9% are alive and have not yet had chemotherapy. Due to the frequent use of rituximab in current clinical practice, a recent study has evaluated whether the use of the "watch-and-wait" approach is more effective than the use of rituximab to delay the need for chemotherapy or radiotherapy in patients with advanced-stage, low tumor burden follicular lymphoma. Immediate treatment with rituximab significantly delays disease progression and the time until chemotherapy or radiotherapy compared with a watchful waiting approach.[69] However, an overall survival advantage has not been demonstrated with this approach.

As described above, patients with follicular lymphoma who are followed without therapy sometimes have spontaneous regressions that can be complete while the disease in other patients can convert to a more aggressive histology. Current guidelines suggest that "watch and wait" is an acceptable initial management approach for patients with low-grade follicular lymphoma who are asymptomatic; have no threatened end-organ function, cytopenias secondary to lymphoma, or bulky disease; and in whom the disease is not steadily progressing. If the watchful waiting approach is chosen, the patient should be evaluated at least every 3 to 6 months for 5 years and then annually, so that intervention can occur before serious problems occur.[49]

Single-Agent Rituximab

The approval of rituximab is arguably the most important development in the treatment of NHL. Its initial approval in 1997 was based on an open-label multicenter study that enrolled 166 patients with relapsed or recurrent indolent lymphoma.[70] Rituximab, given IV at a dose of 375 mg/m^2 weekly for 4 weeks, resulted in an overall response of 48% (complete response: 6%, partial response: 42%). The median time to progression for responders was 13.2 months and the median duration of response was 11.6 months. Other studies of single-agent rituximab in patients with relapsed or refractory indolent NHL have reported overall response rates of 40% to 60% and complete response rates of 5% to 10%.[71]

Based on the activity of rituximab in relapsed or refractory patients, it is currently being used as first-line therapy, either alone or in combination with chemotherapy.[71] When given as a single agent to patients with previously untreated indolent NHL, the overall response rate is 60% to 70% and the complete response rate is 20% to 30%. It is interesting to note that many of these patients remain in molecular remission (ie, polymerase chain reaction—negative) at 12 months. Single-agent rituximab is listed as an acceptable option for first-line therapy of follicular lymphoma, particularly for patients who cannot tolerate more intensive chemotherapy regimens.[49]

In patients who respond to rituximab, either alone or combined with chemotherapy, maintenance therapy with single-agent rituximab is often given to prolong the duration of remission. Rituximab is FDA-approved as single-agent maintenance therapy in patients achieving a complete or partial response following induction chemotherapy. The FDA approval was based on a randomized controlled trial in previously untreated patients with advanced-stage follicular lymphoma treated with maintenance rituximab after CVP chemotherapy.[72] After a median follow-up of 11.5 years in the E1496 study, patients with indolent lymphoma receiving maintenance rituximab had longer median progression-free survival than patients on observation (4.8 vs 1.3 years). However, no significant difference in 10-year overall survival between maintenance rituximab and the observation group was observed (67% vs 59%).[73] Maintenance rituximab is expensive and may be associated with serious adverse drug reactions, including an increased risk of grades 3 or 4 infections. The NCCN guideline lists maintenance therapy with rituximab (one dose every 8 weeks for up to 2 years) as an option following first-line therapy for patients initially presenting with a high tumor burden.[49]

Rituximab maintenance following second-line therapy has also been evaluated in patients with relapsed or refractory disease. Two randomized trials

have demonstrated a progression-free survival advantage with rituximab maintenance over observation for patients treated with induction chemotherapy.[74,75] Patients who develop progressive disease during or within 6 months of first-line maintenance rituximab will likely experience little, if any, benefit from maintenance therapy in the second-line setting. The NCCN guideline recommends optional maintenance therapy with rituximab (one dose every 12 weeks for 2 years) for patients who are in remission after second-line therapy.[49]

Most of the adverse drug reactions of rituximab are infusion-related, particularly after the first intravenous infusion, and consist of fever, chills, respiratory symptoms, fatigue, headache, pruritus, and angioedema. Premedication with oral acetaminophen 650 mg and diphenhydramine 50 mg is usually given 30 minutes before rituximab infusion. Duration of infusions may take up to 5 hours. The package insert recommends a step-up infusion rate of rituximab to decrease the risk of infusion-related events. The FDA has approved rapid infusions of rituximab, but they are not recommended in patients with clinically significant cardiovascular disease and high circulating lymphocyte counts (>5,000 cells/mm^3 [5×10^9/L]). Reactivation of hepatitis B has been reported in patients receiving chemotherapy, either alone or combined with rituximab. Hepatitis B testing is recommended in patients who are considering rituximab therapy.[49]

In addition to the intravenous formulation of rituximab, a subcutaneous formulation of rituximab was approved. In this formulation, rituximab is combined with recombinant human hyaluronidase, which allows rituximab to be rapidly dispersed and absorbed after subcutaneous administration. Subcutaneous administration shortens the administration time to 5 to 7 minutes as compared to several hours for the intravenous infusion. FDA approval for the subcutaneous rituximab was based on multiple randomized clinical trials that demonstrated non-inferior rituximab blood concentrations and comparable efficacy and safety for the two formulations.[76,77] Premedication with acetaminophen and antihistamine is still required before each dose of subcutaneous rituximab, and subcutaneous administration should only be considered after patients receive at least one full dose of a rituximab product by intravenous infusion with no severe adverse drug reactions.

Chemoimmunotherapy

Patients with high tumor burden or with disease-related symptoms are typically treated with chemoimmunotherapy, with or without maintenance therapy with an anti-CD20 monoclonal antibody. The rationale for the use of rituximab in combination with conventional agents is based on the clinical activity of both agents/regimens, non–cross-resistant mechanisms of action, non-overlapping toxicities, and synergistic antitumor activity in vitro. In a meta-analysis of randomized controlled trials, patients with indolent lymphoma treated with rituximab and chemotherapy had a significantly higher overall response rate and reduced risk of treatment failure and death.[78] Currently, the most widely used front-line regimen is R-CHOP or bendamustine plus rituximab (BR). Table 155-8 shows the CHOP regimen that is widely used in the treatment of NHL, and the development of the CHOP regimen is described in more detail later in this chapter.

TABLE 155-8

CHOP Regimen

Drug	Dose	Route	Treatment Days
Cyclophosphamide	750 mg/m^2	IV	1
Doxorubicin[a]	50 mg/m^2	IV	1
Vincristine[b]	1.4 mg/m^2	IV	1
Prednisone	100 mg	Oral	1-5
One cycle is 21 days			

[a]Another name for doxorubicin is hydroxydaunorubicin.

[b]Vincristine dose is typically capped at 2 mg.

Bendamustine is an alkylating agent with structural similarities to both alkylating agents and purine analogs. The mechanism of action of bendamustine is different from other alkylating agents and it does not show cross-resistance to other alkylating agents. When used as a single agent, bendamustine shows antitumor activity in relapsed or refractory indolent lymphomas. Overall and complete response rates of 70% to 80% and 30% to 35% have been reported, respectively, in phase II trials.[79] Two randomized, noninferiority studies have reported that BR is noninferior to R-CHOP for indolent lymphomas. In a randomized noninferiority phase III study of patients with advanced indolent lymphoma (with slightly over half follicular lymphoma patients), patients randomized to receive BR had longer median progression-free survival as compared to those in the R-CHOP group. In the subgroup analysis of patients with follicular lymphoma subtype, a significant benefit for progression-free survival was observed with BR versus R-CHOP.[80] In another study, BR was demonstrated to be noninferior to standard therapies (R-CHOP or R-CVP) for overall and complete response rate, with significant improvement in 5-year progression-free survival (65.5% vs 55.8%).[81,82] Both studies also reported that BR was associated with fewer infectious episodes and fewer hematological toxicities such as grade 3 to 4 leukopenia and neutropenia. BR was also associated with less peripheral neuropathy and alopecia.[80,81] However, dermatological toxicities, drug-related hypersensitivities, and vomiting were more common with BR. Based on these results, BR, R-CHOP, and R-CVP are all listed as first-line therapy of follicular lymphoma (category 1).[49]

Obinutuzumab-based chemoimmunotherapy regimens are also approved in the treatment of follicular lymphomas. Obinutuzumab is a humanized anti-CD20 monoclonal antibody developed to have lower complement-dependent cytotoxicity, but greater antibody-dependent cellular cytotoxicity, phagocytosis, and direct B-cell killing than rituximab. Obinutuzumab has been evaluated in both first- and second-line settings. In the first-line trial, patients with previously untreated advanced-stage follicular lymphoma were randomized to receive chemotherapy (CHOP, CVP, or bendamustine) combined with either obinutuzumab or rituximab.[83,84] Patients who achieved a complete or partial remission received maintenance therapy with the same antibody. Although progression-free survival at 3 years favored patients receiving obinutuzumab, overall survival was similar in the two groups. Serious adverse drug reactions such as infusion-related events occurred more frequently in patients receiving obinutuzumab. In the second-line setting, patients with indolent lymphoma (majority being follicular lymphoma) refractory to rituximab were randomized to bendamustine, either alone or combined with obinutuzumab for 6 cycles, followed by maintenance obinutuzumab therapy for 2 years.[85,86] Patients in the obinutuzumab arm had increased progression-free and overall survival as compared to bendamustine monotherapy. The NCCN guidelines list obinutuzumab, combined with chemotherapy, as first-line, second-line, and subsequent therapy options for treatment of follicular lymphoma.[49] To reduce the risk of infusion reactions associated with obinutuzumab, patients should receive premedication including glucocorticoids, acetaminophen, and antihistamines, as well as a step-up infusion rate. In addition, patients receiving obinutuzumab and bendamustine should receive prophylaxis for *Pneumocystis jiroveci* pneumonia and varicella zoster virus.

Lenalidomide

Lenalidomide is an immunomodulating agent that binds to the cereblon E3 ubiquitin ligase complex, which degrades transcription factors and leads to apoptosis of lymphoma cells.[87] The NCCN guidelines list rituximab-lenalidomide as a treatment option for first-line and second-line therapy for treatment of follicular lymphoma.[49] In the first-line setting, one phase III study compared rituximab and lenalidomide versus rituximab and chemotherapy (R-CHOP, BR, or R-CVP) in advanced-stage follicular lymphoma. Patients received different lenalidomide doses and treatment duration (maximum duration of 18 cycles) depending on their response. Maintenance rituximab was given to all patients. Complete response rates at 120 weeks and 3-year progression-free survival were similar in both arms. Safety profiles, however, differed between the two treatment arms, with more patients in the rituximab and chemotherapy group experiencing grade 3 or 4 neutropenia. Patients receiving lenalidomide and rituximab experienced more grade 3 or 4 cutaneous reactions.[88]

The combination of rituximab and lenalidomide was compared to lenalidomide monotherapy in patients with recurrent follicular lymphoma. Compared to lenalidomide monotherapy, the combination had higher overall and complete response rates. The time-to-progression was also longer in the rituximab and lenalidomide group (2.0 vs 1.1 year). Commonly reported toxicities of lenalidomide include neutropenia, fatigue, and thrombosis.[89]

Phosphatidylinositol-3-Kinase (PI3K) Inhibitor

The B-cell receptor signaling pathway plays an important role in the maintenance and progression of FL. The PI3K pathway is downstream from the B-cell receptor and is essential for the survival of FL. Inhibition of PI3K reduces phosphatidylinositol 3,4,5-triphosphate (PIP_3), which is a messenger that affects pivotal cell function including cell proliferation, survival, and metabolism. Among the four isoforms of PI3K, PI3Kδ mediates B-cell receptor signaling and microenvironment support signals that promote the growth and survival of malignant B lymphocytes. Copanlisib, a pan-class I PI3K inhibitor, predominantly targeting PI3Kα and PI3Kδ, is currently approved for treatment of relapsed and refractory follicular lymphoma. Hypertension and hyperglycemia are prominent with copanlisib because of its potent inhibition of PI3Kα. Severe skin infections have also been observed with copanlisib. Copanlisib is a third-line therapy option for patients with relapsed or refractory follicular lymphoma.[49]

Tazemetostat

Among patients with follicular lymphoma, 20% to 25% harbor an activating mutation of the epigenetic regulator EZH2. Such mutation allows the escape from the normal B-cell clonal selection process and allows GCB cells to survive and proliferate. Tazemetostat is a first-generation EZH2 inhibitor and is currently approved for EZH2 mutation positive in relapsed or refractory disease after two prior therapies, or EZH2 wild-type or unknown relapsed/refractory disease in patients who have no satisfactory alternative treatment options. In a trial of tazemetostat, patients with relapsed or refractory FL harboring an EZH2 mutation had a 71% overall response rate, whereas patients without this mutation had an overall response rate of 33%.[90]

T-cell mediated Therapy

Two chimeric antigen receptor (CAR) T-cell therapies have been explored in relapsed/refractory follicular lymphomas. In a phase 2 trial, 84 patients with relapsed/refractory follicular lymphoma after two or more lines of therapy received axicabtagene ciloleucel. The overall response rate was 94%, with 80% having a complete response. The 12-month progression-free and overall survival were 74% and 93%, respectively.[91] Similar efficacy was also observed with tisagenlecleucel.[92]

Mosunetuzumab is a bispecific CD20-directed CD3 T-cell engager, approved for adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. The overall response rate was 80% with 60% achieving complete responses, and the median duration of response was 22.8 months.[93]

T-cell mediated therapies have shown great potential for clinical response in relapsed or refractory follicular lymphoma patients. However, they are associated with high rates of cytokine release syndrome and neurological events including immune effector cell-associated neurotoxicity sydrome, or ICANS.

High-dose chemotherapy, followed by autologous or allogeneic HSCT, is another option for patients with relapsed follicular lymphoma.[94] In patients who are transplanted at the time of initial treatment failure, 5-year event-free survival is about 40% to 50%. Although the rate of recurrence is lower after allogeneic HSCT as compared with autologous HSCT, that benefit is offset by increased treatment-related mortality after allogeneic HSCT. The presence of a survival plateau after allogeneic HSCT suggests that some patients may be cured of their disease.

A recent study has evaluated the role of HSCT in relapsed/refractory follicular lymphoma following disease relapse after prior rituximab-based therapy. Allogeneic HSCT was associated with an increased risk of death on analysis. Autologous HSCT, on the other hand, was associated with a 3-year overall survival rate of 87%.[95] The current NCCN guideline lists autologous HSCT as an appropriate consolidative therapy for patients achieving second or third remission.[49] However, emerging data suggest that patients transplanted after their first or second relapse could achieve better outcomes than those who receive transplants later in their course of illness.[96]

Diffuse Large B-Cell Lymphoma

The DLBCLs are the most common lymphoma in the International NHL Classification Project, accounting for about 30% of all NHLs.[63] DLBCLs are characterized by the presence of large cells, which are similar in size to or larger than tissue macrophages and usually more than twice the size of normal lymphocytes. The median age at the time of diagnosis is in the seventh decade, but DLBCL can affect individuals of all ages, from children to older adults. Patients often present with a rapidly enlarging symptomatic mass, with B symptoms in about 30% to 40% of cases.[49] About 30% to 40% of patients with DLBCL present with extranodal disease; common sites include the head and neck, gastrointestinal tract, skin, bone, testis, and CNS. DLBCL is the most common type of diffuse aggressive lymphomas, which are characterized by an aggressive clinical behavior that leads to death within weeks to months if the tumor is not treated. Diffuse aggressive lymphomas are also sensitive to many chemotherapeutic agents, and some patients treated with chemotherapy can be cured of their disease.

Several factors correlate with response to chemotherapy and survival in patients with aggressive lymphoma. Because the IPI was originally developed based on patients with aggressive lymphoma, the IPI score correlates with prognosis (see Table 155-7).[52] As described above, the revised NCCN-IPI score may more accurately predict prognosis in patients receiving rituximab-containing combination chemotherapy.[53]

Therapy of DLBCL is based on the Ann Arbor stage, IPI (or revised IPI) score, and other prognostic factors.[49] About one-half of patients present with localized (stage I or II) disease. However, many patients present with large bulky masses (ie, larger than 10 cm), and patients with bulky stage II disease are treated with the same approach used for patients with advanced disease (stage III or IV).

Treatment of Localized Disease (Stages I and II)

11 Before 1980, radiation therapy was the primary treatment for patients with localized DLBCL. Five-year disease-free survival with radiation therapy alone was about 50% and 20% in patients with stage I and stage II disease, respectively.[49] Randomized trials in the 1980s showed that radiation therapy followed by chemotherapy resulted in significantly longer disease-free and overall survival as compared with radiation therapy alone. Other studies reported excellent results with a short course of chemotherapy (three cycles) followed by involved-field radiotherapy or six to eight cycles of CHOP chemotherapy, with or without consolidation radiotherapy. With either of these approaches, 5-year progression-free survival was more than 90% for patients with stage I disease and about 70% for patients with stage II disease.[49]

Because the most effective approach was not clear, the SWOG performed a randomized trial that compared three cycles of CHOP and involved-field radiotherapy or six cycles of CHOP in patients with stage I and nonbulky stage II aggressive lymphoma.[97] Patients treated with three cycles of CHOP plus radiotherapy had significantly better 5-year progression-free and overall survival with a lower incidence of life-threatening toxicity than patients treated with CHOP alone. However, with longer follow-up, the differences in progression-free or overall survival were no longer significant between the two arms.

In the rituximab era, most patients with localized disease are treated with either three to four cycles of R-CHOP followed by radiotherapy or six to eight cycles of R-CHOP with no radiotherapy. Although these two treatment options have not been directly compared in a randomized controlled trial, observational data show similar 5-year overall survival in patients with stage I and II DLBCL. Patients who received the abbreviated course of R-CHOP

plus radiotherapy experienced less acute toxicity and a lower risk of requiring second-line therapy.[98] Based on these findings, three cycles of R-CHOP followed by locoregional radiation is recommended for patients with localized, nonbulky DLBCL. Alternatively, if the disease presents at sites where radiotherapy may lead to significant morbidity, six cycles of R-CHOP without radiation can be considered.[49]

A recent study has examined the use of interim PET scans to determine the need for radiotherapy. Patients with a negative interim PET scan received four cycles of R-CHOP alone with no radiotherapy while those with a positive PET scan were subsequently treated with radiotherapy and ibritumomab tiuxetan. Patients with both positive and negative interim PET scans demonstrated similarly excellent survival outcomes, suggesting the potential role of interim PET scans to guide treatment of localized DLBCL.[98]

Treatment of Advanced Disease (Bulky Stage II, Stages III, and IV)

It has been known since the late 1970s that intensive combination chemotherapy can cure some patients with disseminated DLBCL.[46] Initial studies with cyclophosphamide, vincristine (Oncovin®), and prednisone or prednisolone (COP; same as CVP) produced a plateau on the survival curve of just 10%, with a median survival of less than 1 year. Based on the activity of single-agent doxorubicin, McKelvey et al. developed the CHOP regimen (see Table 155-8).[99] A few years later, a SWOG study showed that CHOP was more active than COP, and CHOP chemotherapy rapidly became the treatment of choice for patients with aggressive lymphomas.[100] Studies in larger numbers of patients showed that about 50% of patients had a complete remission to CHOP chemotherapy, and 50% to 75% of the patients who had a complete response (about one-third of all patients) experienced long-term disease-free survival and cure of their disease.

To improve these results, many investigators used several approaches to develop second- and third-generation regimens in the 1980s. Results of phase II trials suggested that these second- and third-generation regimens were more active than CHOP, with slightly higher complete response rates and improved disease-free survival rates. However, they were also more difficult to administer, more toxic, and more expensive. Based on these results, many oncologists adopted one of these second- or third-generation combination regimens as their standard regimen for patients with advanced aggressive lymphomas.

Many randomized studies have compared different combination regimens in patients with aggressive lymphoma. Although the results of these studies show that no one regimen is superior to another, they demonstrate the superiority of anthracycline-containing regimens over those that do not contain an anthracycline. In the largest and most widely cited study, the SWOG initiated a randomized trial in 1986 that compared CHOP to three of the most commonly used third-generation regimens in patients with advanced NHL. At the time of the initial publication (median follow-up: 35 months), no differences in disease-free and overall survival were observed between the four groups.[101] Furthermore, no significant differences in disease-free or overall survival were observed in any subgroup of patients. But the risk of treatment-related mortality was higher in patients receiving one of the third-generation regimens. Extended follow-up of that trial shows that about 35% of patients who participated in that trial are probably cured of their disease, regardless of the initial combination chemotherapy regimen. Interestingly, the overall survival is about 10% higher than the disease-free survival, which probably reflects the effectiveness of salvage high-dose chemotherapy with autologous HSCT (see the "Treatment of Refractory or Relapsed Disease" section).

Based on the lack of survival benefit with the newer combination chemotherapy regimens, the less-complicated and less-expensive CHOP regimen was considered as the treatment of choice for most patients with DLBCL and other aggressive NHLs for many years. Even with CHOP chemotherapy, however, less than 50% of patients with DLBCL were cured of their disease and most patients who relapse after an initial response do so in the first 2 years. New treatment approaches were needed.

Based on the encouraging results of R-CHOP in indolent lymphomas, several studies evaluated this combination in aggressive lymphomas. The first randomized controlled trial that established the efficacy of R-CHOP in advanced-stage DLBCL showed that R-CHOP significantly increased complete response rates and overall survival in older adults (≥60 years old) as compared with CHOP alone (discussed in the "Treatment of Older Patients with Advanced Disease" section).[102] Although the results of that study established R-CHOP as standard therapy in older patients, the role of R-CHOP in the treatment of younger patients was not clear. That issue was addressed in the MabThera International Trial, which enrolled younger (18-60 years old) patients with good-prognosis DLBCL.[103] Patients randomized to receive rituximab plus CHOP-like chemotherapy had significantly higher complete response rates (86% vs 68%) and longer 3-year event-free and overall survival (79% vs 59%; HR 0.44 and 93% vs 84%; HR 0.40, respectively). Updates from the study cohort indicate that the survival benefits of adding rituximab are sustained at 6 years with no increase in the incidence of secondary

malignancies.[104] Based on these trial results, rituximab received FDA approval for first-line treatment in combination with CHOP or CHOP-like chemotherapy and R-CHOP is recommended for all patients with advanced-stage DLBCL in the current NCCN guideline.[49]

Several studies attempted to improve treatment results by increasing chemotherapy dose (ie, dose-intensity), shortening the interval between chemotherapy cycles (ie, dose-density), or both. Because of the increased risk of severe neutropenia, these treatment approaches require growth factor support. Dose-dense chemotherapy, where the interval between cycles is shortened from 3 to 2 weeks, has been evaluated in randomized trials. Before the rituximab era, event-free, and overall survival rates were longer with biweekly CHOP-14 compared to standard CHOP-21 every 21 days.[105] However, long-term follow-up data show that with the addition of rituximab, the survival benefit associated with a dose-dense schedule is not superior to that of R-CHOP-21.[106,107] In one of the trials conducted in older adults, the incidence of severe neutropenia was significantly higher despite an increased use of granulocyte colony-stimulating factor.[107]

Treatment outcomes for high-risk patients according to the IPI (or revised IPI) score are unsatisfactory. High-risk groups generally include all patients older than 60 years and those with an IPI score of 3 or more (or an age-adjusted IPI score of ≥2). Since progression-free survival is only about 50% in these high-risk patients treated with R-CHOP, other more aggressive treatments, preferably as part of a clinical trial, should be considered in these patients.

One approach is to give high-dose chemotherapy with autologous HSCT as intensive consolidation in high-risk patients with DLBCL who achieve a remission with standard chemotherapy. This approach improves progression-free survival in patients with high-risk disease (age-adjusted IPI score of ≥2) who have a response to CHOP-based chemotherapy.[49]

In summary, all patients with bulky stage II, stage III, or stage IV disease should be treated with R-CHOP or rituximab and CHOP-like chemotherapy until a complete response is achieved (usually four to six cycles).[49] The use of long-term maintenance therapy following a complete response has not been shown to improve overall survival. Treatment outcomes for high-risk patients according to the IPI (or revised IPI) score are unsatisfactory and alternative treatment approaches, preferably as part of a clinical trial, should be considered in these patients. High-dose chemotherapy with autologous HSCT should be considered in high-risk patients who respond to standard chemotherapy and are candidates for autologous HSCT.[49]

Treatment of Older Patients with Advanced Disease

More than one-half of patients with NHL are older than 60 years of age at diagnosis, and about one-third are older than age 70 years. The International Non-Hodgkin Lymphoma Prognostic Factors Project showed that patients older than 60 years had a significantly lower complete response rate and overall survival.[52] The reasons for the poorer outcome in older adults are not clear. Older patients do not tolerate intensive chemotherapy as well as younger patients, and some studies report that older patients have a higher risk of treatment-related mortality. As a result, many clinicians treat older adults with reduced dose or less-aggressive chemotherapy regimens. In general, these less-intensive regimens use anthracyclines with less cardiotoxicity than doxorubicin, substitute mitoxantrone for doxorubicin, or use short-duration weekly therapy.[108]

Over the past few years, several nonrandomized and randomized trials have evaluated different treatment approaches in older patients with aggressive NHL. The results of these studies suggest that carefully selected older adults with good performance status and without significant comorbidities can tolerate aggressive anthracycline-containing regimens as well as younger patients. These patients should be treated initially with full-dose R-CHOP or similar regimens; dosages can be reduced later if severe toxicity occurs. Hematopoietic growth factors may allow older adults to maintain dose intensity.[108]

The combination therapy, R-CHOP, has replaced CHOP as standard treatment for older adults with aggressive lymphoma, based on the results of the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study.[102] In that study of older adults with DLBCL, patients who were randomized to receive R-CHOP had a significantly higher complete response rate and longer event-free and overall survival as compared with those who received CHOP. After 10 years of follow-up, progression-free survival was significantly longer among those who received R-CHOP than CHOP.[102] A higher risk of death or secondary cancer was not observed with the addition of rituximab to CHOP after 10 years of follow-up. In another randomized controlled trial conducted primarily in the United States (Eastern Cooperative Oncology Group 4494), older adults (≥60 years old) who received rituximab, either as induction or maintenance with CHOP chemotherapy, had significantly longer failure-free survival as compared with those not given rituximab during their treatment course.[109] Maintenance therapy with single-agent rituximab did not provide any additional benefit in patients who received R-CHOP as

induction therapy. Rituximab is given differently in the two studies. In the GELA study, rituximab is given on day 1 (the same day that cyclophosphamide, doxorubicin, and vincristine are administered) with each cycle of CHOP chemotherapy.[102] In the Eastern Cooperative Oncology Group 4494 study, R-CHOP was modeled after the regimen developed by Czuczman et al.: two doses of rituximab are given before cycle 1, and one dose is given before cycles 3, 5, and 7 (if administered).[110] In most NHL protocols and in clinical practice, rituximab is given on day 1 of each cycle of CHOP chemotherapy.

Previous trials have evaluated different drugs, including rituximab, as maintenance treatment in DLBCL but have failed to show survival benefits. Lenalidomide as maintenance in older adults (60-80 years old) who had responded to R-CHOP was recently evaluated in the REMARC trial. Maintenance lenalidomide for 24 months prolonged progression-free survival but did not improve overall survival and was associated with a higher premature discontinuation rate.[111] Based on these results, lenalidomide is an option if maintenance therapy is considered in older adults who have responded to treatment.[49]

Treatment of Refractory or Relapsed Disease

12 Although many patients with aggressive NHL experience long-term survival and cure with intensive chemotherapy, about 10% to 20% of patients fail to achieve a complete remission and about 20% to 30% of patients who do achieve a complete remission will subsequently relapse. Therefore, about 30% to 40% of all patients with aggressive NHL will require salvage therapy at some point during their disease course. Response to salvage therapy depends on the initial responsiveness of the tumor to chemotherapy. Patients who achieve an initial complete remission and then relapse generally have a better response to salvage therapy than those who are primarily or partially resistant to chemotherapy.[112]

Many conventional-dose salvage chemotherapy regimens have been used in patients with relapsed or refractory NHL. Many patients who respond to salvage therapy (ie, chemosensitive relapse) will then receive high-dose chemotherapy with autologous HSCT. To avoid cross-resistance, most salvage regimens incorporate drugs not used in the initial therapy. Some of the more commonly used salvage regimens include ICE, dexamethasone, cytarabine, cisplatin (DHAP), etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP), mesna, ifosfamide, mitoxantrone, etoposide (MINE), gemcitabine, dexamethasone, and cisplatin (GDP) and no one regimen is superior to any other regimen.[113] With these salvage regimens, about 30% to 50% of patients achieve a complete response, with a median duration of remission of 1 to 2 years. Only about 5% to 10% of patients will have long-term disease-free survival.[112]

Rituximab is sometimes added to these salvage regimens. It is recommended, however, to exclude rituximab in second-line therapy if the patient's disease is refractory or if the duration of remission is less than 6 months. One study (CORAL study) compared two salvage regimens (R-ICE and R-DHAP) in patients with relapsed or refractory DLBCL, followed by autologous HSCT.[114] No significant difference in 3-year event-free survival or overall survival was observed between R-ICE and R-DHAP. However, patients who had received prior rituximab and experienced early relapse (defined as less than 12 months after diagnosis) had a poor prognosis. New treatment strategies are needed to improve the response rates of salvage regimens.

To improve the cure rate, many studies have evaluated high-dose chemotherapy with autologous HSCT as intensive consolidation therapy in patients who respond to salvage therapy. In the PARMA study, patients with relapsed aggressive NHL who had a response to DHAP salvage therapy were randomized to receive either high-dose chemotherapy or continued DHAP therapy.[115] Patients who received high-dose chemotherapy had significantly longer 5-year disease-free survival (46% vs 12%) and overall survival (53% vs 32%) than those treated with conventional salvage therapy. Further analysis of that study showed that patients who relapsed within 12 months of their initial diagnosis were less likely to benefit from high-dose chemotherapy than patients who relapsed after 12 months. Based on a review of the available evidence, including the PARMA study, high-dose chemotherapy with autologous HSCT is considered to be the treatment of choice in younger patients with chemotherapy-sensitive relapse.[49] High-dose chemotherapy with autologous HSCT is not recommended in patients with untested or chemotherapy-refractory relapse.

In patients who have failed multiple lines of treatment, several agents have been studied, including selinexor and CAR T-cell therapy. CAR T-cell therapy is a type of adoptive immunotherapy where the patient's own T-lymphocytes are collected, modified genetically in the laboratory to target antigens on malignant cells, and then adm inistered back to the patient by infusion.[116] Examples of CAR T-cell therapy are axicabtagene ciloleucel and lisocabtagene maraleucel. Both treatments have ben approved by the FDA for relapsed DLBCL after failure of one line of systemic treatment based on favorable survival outcomes from phase III trials ZUMA-7 and TRANSFORM, which demonstrated significantly improved median event-free survival among patients who received axicabtagene ciloleucel and lisocabtagene maraleucel, respectively, compared to patients who received salvage

chemoimmunotherapy.[117,118] Another CAR T-cell therapy tisagenlecleucel is indicated for relapsed and refractory DLBCL only after failure of two or more lines of systemic treatment.

CAR T-cell therapies are associated with a high incidence of cytokine release syndrome, which is characterized by fever, hypoxia, and hypotension, and may require the use of vasopressors in severe cases. Severe neurological toxicities such as encephalopathy and seizures can also occur, usually within days of T-cell infusion. While mild episodes can be symptomatically managed, moderate-to-severe grades of cytokine release syndrome and neurological toxicities may require immunosuppressants including tocilizumab and corticosteroids.[49,116,119]

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is found in 6% of cases in the International Lymphoma Classification Project.[63] The chromosomal translocation t(11;14) occurs in most cases of MCL. MCL usually occurs in older adults, particularly in men, and most patients have advanced disease at the time of diagnosis (see Table 155-6). Extranodal involvement is found in about 90% of cases. The course of the disease is moderately aggressive; the median overall survival is about 3 years, with no evidence of a survival plateau.

Both aggressive and less-aggressive chemotherapy regimens have been evaluated in patients with disseminated MCL. One widely used aggressive combination regimen is cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine (hyperCVAD) with or without rituximab. Overall response rates to these regimens are about 90%, with long-term progression-free survival rates of 59% and 35% at 5 and 10 years, respectively.[120] Less-aggressive regimens are often used for patients who are not candidates of HSCT. Because MCL usually expresses CD20, rituximab, either alone or combined with CHOP and bendamustine, has been used with some success in patients with newly diagnosed and relapsed MCL.[80,121] In a phase III study, BR was compared to R-CHOP for first-line therapy in patients with advanced follicular, indolent, and MCL. In the MCL subgroup, progression-free survival was higher with BR compared to R-CHOP up to 5 years after treatment completion, and it is associated with less hematologic toxicities.[80–82] However, a higher number of secondary malignancies were observed in the BR group during long-term follow-up.[82] Another less-aggressive option that has been found to yield favorable results was lenalidomide in combination with rituximab, with 5-year progression-free and overall survival rates of 63.9% and 77.4%, respectively.[122] Bortezomib (Velcade®), in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone, (VR-CAP, similar to R-CHOP regimen but with bortezomib replacing vincristine) is also indicated for newly diagnosed MCL.[123] In a phase III randomized study, patients with newly diagnosed MCL who were ineligible or not considered for HSCT received R-CHOP or VR-CAP. After a median follow-up of 40 months, median progression-free survival was longer in the VR-CAP arm compared to R-CHOP (24.7 vs 14.4 months). Rates of neutropenia and thrombocytopenia were higher in the VR-CAP group.[123]

Despite the high response rates, MCL is not considered curable with standard chemotherapy. Therefore, younger patients who have an initial response to chemotherapy often undergo autologous or allogeneic HSCT as consolidation therapy. The NCCN guidelines recommend that patients with advanced-stage MCL be treated initially with rituximab and combination chemotherapy, followed by autologous HSCT as first-line consolidation therapy.[49] In patients who respond to autologous HSCT, maintenance rituximab or lenalidomide are options that have been demonstrated to prolong progression-free and overall survival.[124–126] Findings from a prospective study suggest that similar survival benefits are also associated with the use of maintenance rituximab after R-CHOP in older patients who are not candidates for autologous HSCT.[127]

Unfortunately, most patients with MCL eventually relapse and are treated with salvage therapy or enrolled in trials of investigational agents, some of which are directed at molecular targets. First-line regimens such as R-CHOP, VR-CAP, and bendamustine can be considered if they have not been previously given.[49] Bortezomib with or without rituximab is also approved for the treatment of MCL that has relapsed after at least one prior therapy.

Novel agents that have been approved for the treatment of relapsed or refractory MCL include the Bruton tyrosine kinase (BTK) inhibitors ibrutinib, acalabrutinib, zanubrutinib and pirtobrutinib. In a phase III randomized trial, ibrutinib had a higher response rate and longer median duration of response with a more favorable safety profile than temsirolimus.[128] Addition of rituximab to ibrutinib was further evaluated in a phase II trial that reported a response rate of 88%, with a median duration of response of 46 months.[129] Other oral BTK inhibitors, acalabrutinib and zanubrutinib, have demonstrated overall response rates of more than 80% in phase II trials in patients with relapsed and refractory MCL.[130] The most common adverse drug reactions of BTK inhibitors include diarrhea and fatigue. Since cytopenias are also common, complete blood counts should be monitored monthly while patients are on treatment. Bleeding may rarely occur during the first 6 months of BTK inhibitor therapy. Cases of new-onset atrial fibrillation have also been reported. A CAR T-cell therapy, brexucabtagene autoleucel, has also been approved for the treatment of relapsed and

refractory mantle cell lymphoma in adult patients. Approval was granted based on ZUMA-2, a single-arm trial that demonstrated a response rate of 93% and a 12-month overall survival rate of 83%.[131]

EVALUATION OF THERAPEUTIC OUTCOMES

Hodgkin lymphoma and NHLs tend to respond well to radiation, chemotherapy, and biologic therapy. The goal of therapy for patients with Hodgkin lymphoma and aggressive NHL is long-term survival and cure. The therapeutic goal in patients with indolent NHLs is less clear because of the indolent nature of the disease and the lack of convincing evidence showing that therapy prolongs survival. Therapeutic responses should be evaluated based on physical examination, radiologic evidence, PET/CT scanning, and other positive findings at baseline. The current standard of care to evaluate response to treatment in Hodgkin lymphoma, follicular lymphoma, and DLBCL is PET imaging. As described earlier, the 5-point scale is recommended for PET-CT interpretation where a Deauville score of 1, 2, or 3 (uptake less than or equivalent to liver) indicates complete response, even in the presence of a persistent mass. If salvage treatment is considered based on a metabolically active residual mass, a biopsy or follow-up scan should be considered.[50] CT is advised for other lymphomas with low or variable FDG avidity. The rapidity of response to therapy in patients with indolent NHL depends on the choice of therapy. Early interim PET-CT scans may also possess prognostic value in patients with advanced Hodgkin lymphoma.[18] In NHL, the prognostic value of interim PET-CT scans is less established and they are currently not recommended to guide changes in therapy.[49] Patients should be clinically monitored every 3 months for 2 years, then every 6 to 12 months as appropriate. Surveillance scans after disease remission has been achieved are currently not advised, especially in Hodgkin lymphoma and DLBCL, but they can be considered in the event of equivocal findings at the end of treatment or in indolent lymphomas with residual disease.[50]

CONCLUSION

Hodgkin lymphoma and NHL are the two primary histologic classifications of lymphoma. Hodgkin lymphoma is defined by the presence of Reed–Sternberg cells. Restaging PET-CT serves to guide patient-specific treatment plans primarily comprised of combination chemotherapy with or without radiation therapy. The primary combination chemotherapy utilized is ABVD. NHL is a much more heterogeneous group of malignancies and is classified by a combination of morphology, immunophenotype, genetic features, and clinical features. Treatment response is often based on the aggressiveness of the NHL. Aggressive NHLs, such as DLBCL, can often be cured with combination chemoimmunotherapy with R-CHOP. Indolent NHLs, such as follicular lymphoma, are often uncurable but can be managed long-term with a variety of different treatment approaches. In the relapsed setting, salvage chemoimmunotherapy is used along with high-dose chemotherapy followed by autologous HSCT. Several novel agents, including the CAR T-cell therapy is a new approach for NHL and an area of ongoing research.

ABBREVIATIONS

A-AVD	brentuximab vedotin (Adcetris®), doxorubicin (Adriamycin®), vinblastine, and dacarbazine
ABC	activated B-cell–like
ABV	doxorubicin (Adriamycin®), bleomycin, vinblastine
ABVD	doxorubicin (Adriamycin®), bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
AIDS	acquired immune deficiency syndrome
BEACOPP	bleomycin, etoposide, doxorubicin (Adriamycin®), cyclophosphamide, vincristine (Oncovin®), procarbazine, and prednisone
BR	bendamustine and rituximab

BTK	Bruton tyrosine kinase
CAR	chimeric antigen receptor
CHOP	cyclophosphamide, doxorubicin, vincristine (Oncovin®), prednisone
COP	cyclophosphamide, vincristine (Oncovin®), and prednisone or prednisolone
COPP	cyclophosphamide, vincristine, procarbazine, and prednisone
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
DHAP	dexamethasone, cytarabine, cisplatin
DLBCL	diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
ESHAP	etoposide, methylprednisolone, cytarabine, cisplatin
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FLIPI	Follicular Lymphoma International Prognostic Index
GCB	germinal center B-cell like
GDP	gemcitabine, dexamethasone, cisplatin
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GHSG	German Hodgkin Study Group
GVD	gemcitabine, vinorelbine, and pegylated liposomal doxorubicin
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
Hyper CVAD	cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine

ICE	ifosfamide, carboplatin, and etoposide
IFRT	involved-field radiation
IPI	International Prognostic Index
IPS	International Prognostic Score
ISRT	involved-site radiation therapy
JAK–STAT	Janus kinase–signal transduction and transcription
KSHV	Kaposi sarcoma–associated herpesvirus
LDH	lactate dehydrogenase
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
MINE	mesna, ifosfamide, mitoxantrone, etoposide
MMAE	monomethyl auristatin
MOPP	mechlorethamine, vincristine, procarbazine, and prednisone
MOPPEBVCAD	mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
PET	positron emission tomography
PI3K	phosphatidylinositol-3-kinase
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine (Oncovin®), prednisone
REAL	Revised European-American Classification of Lymphoid Neoplasms
RICE	rituximab, ifosfamide, carboplatin, and etoposide
SEER	surveillance, epidemiology, and end results
SWOG	Southwest Oncology Group
WHO	World Health Organization

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SELF-ASSESSMENT QUESTIONS

1. What is the first-line treatment of choice for a patient with Stage IIA Classical Hodgkin lymphoma?
   A. ABVD chemotherapy +/− Involved field radiation
   B. Surgical resection
   C. Involved field radiation alone
   D. All of the above
2. Which of the following is *not* a “B” symptom?
   A. Night sweats
   B. Fever
   C. Pruritus
   D. Weight loss (>10%)
3. A 50-year-old white male presents with fatigue, weight loss, and fever and is later diagnosed with Stage IV Hodgkin lymphoma. Additional labs include: Hgb 9.1 g/dL (91 g/L; 5.65 mmol/L), WBC 23,000/µL (23×10^9/L), Plt 120,000/µL (120×10^9/L), albumin 3.2 g/dL (32 g/L), SCr 1.1 g/dL (97 µmol/L), and bili 1 mg/dL (17.1 µmol/L). What would be the most effective initial risk-adapted treatment for this patient?
   A. COPP/ABVD
   B. ABVD
   C. MOPP
   D. Escalated dose BEACOPP

4. A 22-year-old male with Stage IV Hodgkin lymphoma wants to retain fertility. What chemotherapy regimen would you recommend for this patient?

   A. ABVD

   B. MOPP

   C. ChlVPP

   D. MOPP/ABV hybrid

5. A 25-year-old female is diagnosed early-stage Hodgkin lymphoma with favorable prognosis. She is going to receive four cycles of ABVD. What is the overall survival rate for this patient?

   A. >10%

   B. >30%

   C. >60%

   D. >90%

6. Which of the following long-term toxicities is a greater concern for escalated dose BEACOPP as compared with ABVD?

   A. Cardiac disease

   B. Secondary malignancy

   C. Interstitial pulmonary fibrosis

   D. Renal insufficiency

7. Which of the following is true when one compares the A-AVD regimen versus the ABVD regimen?

   A. Replaces the bleomycin for brentuximab vedotin

   B. Should not be used in patients with baseline pulmonary fibrosis

   C. Replaces the bleomycin for actinomycin

   D. Has a lower risk of peripheral neuropathy

8. Brentuximab is a monoclonal antibody targeted against lymphoma cells. What is the molecular target of brentuximab?

   A. CD20

   B. CD30

   C. CD52

   D. LAP (lymphoma-associated protein)

9. Which of the following classification systems is currently used for non-Hodgkin lymphoma?

   A. REAL-WHO

   B. Luke-Collins

   C. Kiel

D. International Working Formulation

10. What is the clinical objective of the IPI and FLIPI score?

A. To classify the lymphoma as either indolent or aggressive

B. To predict likelihood for conversion to a more aggressive histology

C. To classify the lymphoma into molecular subtypes

D. To predict prognosis (ie, survival)

11. What is the appropriate treatment for a newly diagnosed patient with advanced-stage follicular lymphoma?

A. Obinutuzumab and bendamustine

B. Rituximab and lenalidomide

C. Rituximab and CHOP chemotherapy (R-CHOP)

D. All of the above are appropriate treatment options, depending on patient and tumor characteristics and patient and physician preferences

12. Which of the following terms best describe lenalidomide?

A. Monoclonal antibody

B. Immunomodulator

C. Immunotherapy

D. Recombinant protein

13. What is the appropriate treatment for a newly diagnosed patient with advanced-stage diffuse large B-cell lymphoma?

A. Rituximab and CHOP chemotherapy (R-CHOP)

B. Bendamustine

C. CHOP chemotherapy

D. Idelalisib

14. Which of the following statements best describe the results of appropriate treatment in patients with advanced-stage diffuse large B-cell lymphoma?

A. About 30% to 60% of patients can be cured of their cancer

B. About 60% to 90% of patients can be cured of their cancer

C. Patients are not cured of their disease, but they will probably live longer

D. Patients will probably not live longer, but they may have improved quality of life

15. Which of the following chemotherapy regimens warrant primary prophylaxis with granulocyte colony-stimulating factor?

A. Dose-dense CHOP

B. Escalated-dose BEACOPP

C. BEACOPP-14

D. All of the above

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** ABVD chemotherapy +/− involved field radiation therapy remains the most well studied and clinically proven therapy in most patients with early-stage disease. Although other chemotherapy regimens may be an option, ABVD was the only answer that involved chemotherapy. Historically radiation therapy was primarily used for early-stage Hodgkin lymphoma, but chemotherapy has demonstrated fewer long-term complications.

2. **C.** By definition, B symptoms include unexplained fevers >38°C (100.4 °F), drenching night sweats, and/or weight loss of >10% body weight within 6 months of diagnosis. Pruritus and alcohol intolerance are findings that can occur with Hodgkin lymphoma but are not considered B symptoms.

3. **D.** The key to this question is the "risk adapted" portion. Escalated dose BEACOPP allows doses to be increased according to the patient's tolerance and response. This can be used in a select group of patients with high IPS scores and age less than 60. This patient's poor-risk features include albumin <4 g/dL (40 g/L), hemoglobin <10.5 g/dL (105 g/L; 6.52 mmol/L), male, stage IV disease, age >45 years, white blood cell count >15,000 cells/mm^3 (15×10^9/L), with an IPI score >4.

4. **A.** MOPP and MOPP-like regimens (which include ChlVPP and MOPP/ABVD hybrids) deliver large amounts of alkylating agents. Alkylating agents are known to cause decreased fertility. Of the regimens available to choose from in this question, ABVD offers the lowest exposure to alkylating agents.

5. **D.** Hodgkin lymphoma boasts one of the highest cure rates of all cancer diagnoses. Cure rates with initial and subsequent therapies in patients with early-stage Hodgkin lymphoma are in the 90% to 95% range. Cure rates in patients with stage III and IV disease are lower, but still in the 60% to 80% range.

6. **B.** As with Question 4 above, increasing exposure to alkylating agents increases both the risk of sterility and secondary malignancies. Additionally, topoisomerase II inhibitors are associated with secondary malignancies. The key medications in escalated dose BEACOPP that contribute to the risk of secondary malignancies include etoposide, doxorubicin, cyclophosphamide, and procarbazine.

7. **A.** The A-AVD regimen was designed to replace bleomycin with brentuximab vedotin. Bleomycin is known to cause pulmonary fibrosis and should be avoided in patients with known baseline pulmonary fibrosis. Brentuximab vedotin can cause peripheral neuropathy, and when combined with doxorubicin, vinblastine and dacarbazine, has a higher incidence of neuropathy versus ABVD.

8. **B.** Brentuximab targets CD30. Most classical Hodgkin lymphoma cells express or overexpress CD30 on their cell surface.

9. **A.** The REAL-WHO classification system is currently used for classifying the various subtypes of non-Hodgkin lymphomas. The system categorizes lymphoid malignancies into B-cell lymphomas and T-cell (and natural killer cell) lymphomas.

10. **D.** Both IPI and FLIPI assist clinicians to predict the prognosis of a patient with non-Hodgkin lymphoma. IPI is used for diffuse large B-cell lymphomas, while FLIPI is used for follicular lymphomas.

11. **D.** Many therapeutic options are available for a newly diagnosed patient with advanced-stage follicular lymphoma, and the choice of therapy depends on patient and tumor characteristics, as well as patient and physician preferences. Refer "Treatment of Advanced Disease (Stages II Bulky, III, and IV)" section under Non-Hodgkin Lymphoma for more information.

12. **B.** Lenalidomide is an immunomodulating agent that is used for patients with indolent non-Hodgkin lymphomas.

13. **A.** R-CHOP is one of the first-line chemotherapies recommended by current NCCN guidelines for the treatment of newly diagnosed diffuse large B-cell lymphoma.

14. **B.** Based on the results of landmark RCHOP studies such as the MabThera International Trial (MiNT), RCHOP has improved the cure rate of diffuse large B-cell lymphoma among patients with advanced disease from about 60% to 90%. See the "Diffuse Large B-Cell Lymphoma" section and its subsection "Treatment of Advanced Disease" for more details.

15. **D.** Granulocyte colony-stimulating factor should be given for primary prophylaxis in chemotherapy regimens that have a risk of febrile neutropenia of more than 20%. This includes dose-dense RCHOP, escalated-dose BEACOPP, and BEACOPP-14.