CHAPTER

21

Non-Hodgkin lymphoma

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Overview of lymphocyte development and classification of lymphoid malignancies

The lymphoid system forms the backbone of the human immune system, contributing to both the innate (non-specific) immune response through natural killer (NK) cells and the adaptive (specific) immune response through B- and T-cells. B- and T-cell lymphomas account for the vast majority of non-Hodgkin lymphomas, neoplasms that originate in these cells. Knowledge of B- and T-cell development is important in understanding the biology and, in turn, providing insight into the behavior of the numerous subtypes of these lymphomas that are derived from their normal B- and T-cell counterparts.

B-cell development and the biology of B-cell lymphomas

Common lymphoid progenitors in the bone marrow derived from hematopoietic stem cells are the source of B- and T-cells. Unlike T-cells, full B-cell maturation occurs in the bone marrow and begins with recombination of the *V*, *D*, and *J* gene segments of the immunoglobulin heavy chain (IgH) followed by the light chain genes in order to generate a functional immunoglobulin that is expressed on the cell surface as B-cell receptor (BCR). The survival and maturation of B-cells in the bone marrow, as well as the differentiation of mature B-cells that have exited the bone marrow, is dependent on operative BCR signaling. Importantly, BCR signaling has also been found to be necessary for lymphoma development and evolution with many mature B-cell malignancies showing sensitivity to kinase inhibitors, such as ibrutinib and idelalisib, which disrupt BCR signaling.

Collectively, the primary function of B-cells is to generate a vast diversity of immunoglobulins. Generating this diversity begins with the combinatorial diversity produced from random *V*, *D*, and *J* rearrangements. Combinatorial diversity is amplified by junctional diversity produced by the action of terminal deoxynucleotidyl transferase (TdT) where nucleotides are randomly added or deleted at the sites of *V*, *D*, and *J* fusion. Successful rearrangement of the heavy and light immunoglobulin chains (either kappa or lambda) results in expression of functional IgM and IgD on the surface mature B-cells that exit the marrow. These mature, but antigen naïve, B-cells then gain additional diversity when exposed to antigen in the germinal centers of secondary lymphoid organs such as lymph nodes, mucosa associated lymphoid tissue, or the spleen. Here, somatic hypermutation occurs in the V genes of the heavy and light chains, fine tuning their affinity to their cognate antigens. B-cells expressing immunoglobulin with just the right amount of antigen affinity differentiate to memory B-cells or plasma cells while all the others undergo apoptosis. Finally, class switching also occurs in the germinal center and involves changing the heavy chain that is expressed to produce IgG, IgA, or IgE.

The classification of B-cell lymphomas is based on the observation that malignant B-cells appear to be frozen at particular differentiation stages that reflect their origin and, in part, dictate their biology (Figure 21-1). Distinct stages of B-cell development and differentiation are characterized by distinct cytologic features, expression patterns of differentiation markers, and BCR. These characteristics form the basis of pathologic diagnosis of lymphoid neoplasms. For example, B-lymphoblastic leukemia/lymphoma arises from an

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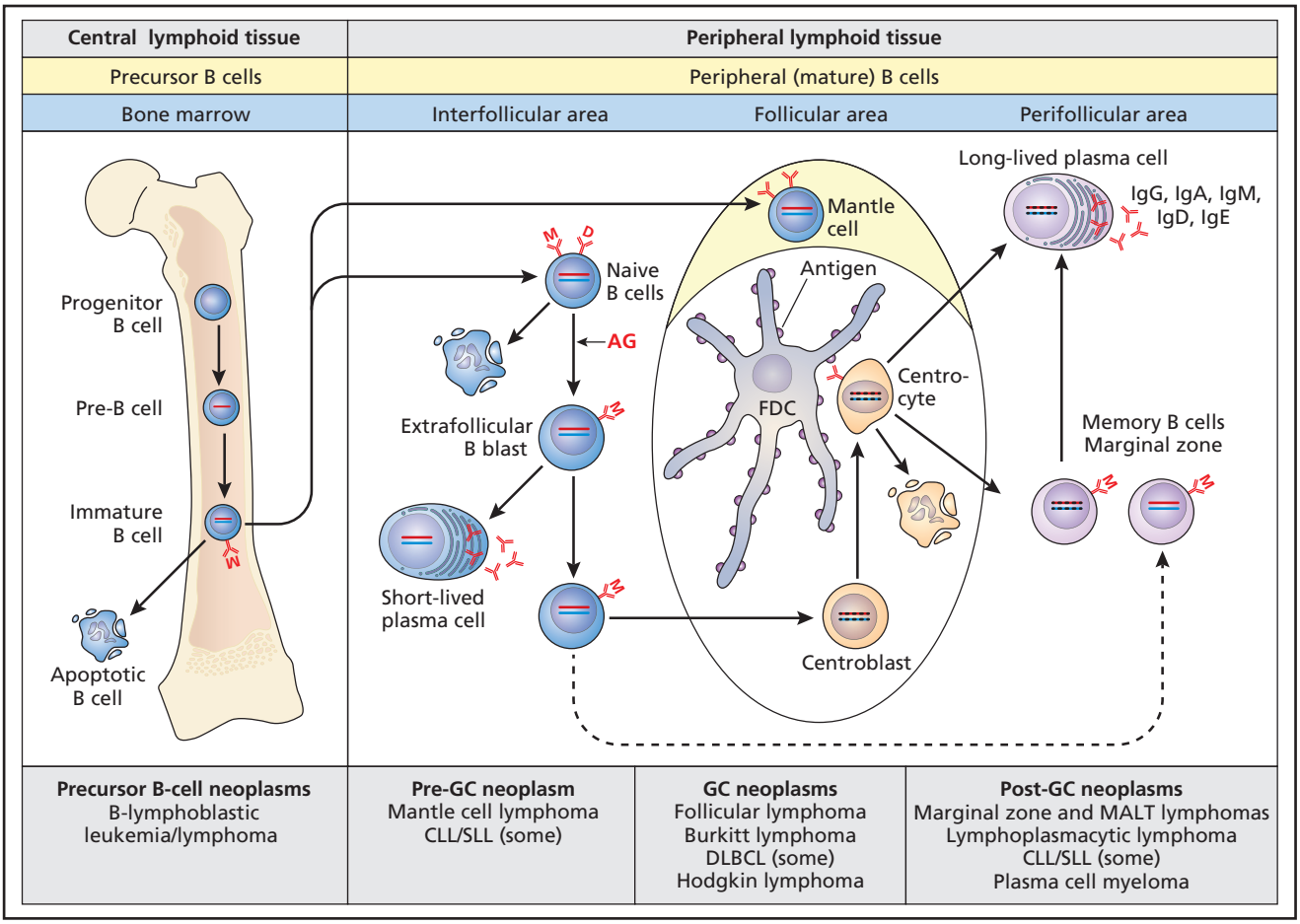

Figure 21-1 Schematic representation of B-cell differentiation (WHO 2008). CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL = diffuse large B-cell lymphoma; GC = germinal center; MALT = mucosa-associated lymphoid tissue. Reproduced with permission from Harald Stein.

immature B-cell (Figure 21-1) and accordingly, diagnosis requires the identification of immature B-cells that have morphologic characteristics of blasts; co-express B-cell markers, such as CD19, with markers of immaturity, such as TdT and CD10; and do not express BCR on their surface. Likewise, follicular lymphoma (FL) arises from a germinal center B-cell (Figure 21-1) and has morphologic characteristics of nodular growth, resembling B-cell follicles, while expressing the germinal center marker CD10 with surface IgM, IgD, IgG or IgA.

The transformation of benign B-cells to their malignant counterparts is closely linked to the mandate of B-cells to generate immunological diversity. Conditions under which malignant transformation is fostered include viral infection, chronic bacterial infection, immune deficiency, and exposure to toxins (Table 21-1). Given the degree to which the immunoglobulin genes of B-cells are subjected to DNA damage in the bone marrow and germinal centers, it is not surprising that reciprocal translocations involving an immunoglobulin gene locus and a proto-oncogene form the hallmark of many types of B-cell lymphoma (Table 21-2).

Table 21-1 Risk factors in the development of non-Hodgkin lymphoma

Viral infection	EBV, HTLV-1, HHV-8, hepatitis C
Bacterial infection	*Helicobacter pylori*
	Chlamydophila psittaci
Impaired/altered immunity	Ataxia-telangiectasia
Congenital disorders	Wiskott-Aldrich syndrome
	X-linked lymphoproliferative syndrome
	Severe combined immunodeficiency
	Other immunodeficiency states
Acquired conditions of immunodeficiency	AIDS (HIV infection)
	Organ or stem cell transplantation
	Aging
	Autoimmune and rheumatologic disease
Environmental or occupational	Herbicides
	Pesticides

Table 21-2 Phenotypic markers and chromosomal translocations in non-Hodgkin lymphomas

NHL	sIg	CD5	CD10	CD20	Other	Cyclin D1	Cytogenetics	Oncogene	Function
CLL/SLL	Weak	+	−	Dim	CD23+ FMC−	−	No diagnostic abnormalities*	−	−
Follicular	++	−	+	+	−	−	t(14;18)	*BCL2*	Anti-apoptosis
Mantle cell	++	+	−	+	CD23− FMC+	+	t(11;14)	Cyclin D1	Cell cycle regulator
Marginal zone/ extranodal marginal zone lymphoma	+	−	−	+		−	t(11;18)	*AP12*−MALT	Resistance to *Helicobacter pylori* treatment
Lymphoplasmacytic lymphoma	++	−	−	+	CD25+/− CD38+/−	−	−	*MYD88*	Proliferation
Hairy cell leukemia	++	−	−	+	CD11c+, CD25+, CD103+	Weak	−	*BRAF*	Proliferation
DLBCL	+	Rare	+/−	+	−	−	t(14;18), t(3;14), t(3;v) Rare t(8;X),	*BCL2* *BCL6* *cMYC* *EZH2*‡ *MYD88*§	Anti-apoptosis Transcription factor Proliferation Histone modifier Proliferation
PMBCL	+	−	−/+	+	CD30+/−	−	t(16;X)†	*CIITA*	MHC class II transactivator
Burkitt lymphoma	+	−	+	+	TdT−	−	t(8;14), t(2;8), t(8;22)	*cMYC*	Transcription factor
ALCL, ALK-positive	−	−	−	−	CD30+, CD2+/−, CD3−/+ EMA+	−	t(2;5)	*ALK*	Tyrosine kinase
ALCL, ALK-negative	−	−	−	−	CD30+, CD2+/−, CD3−/+ EMA−	−	t(6;7)(p25.3;q32.3)	*DUSP22*	Phosphatase

ALCL = anaplastic large-cell lymphoma; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; MALT = mucosa-associated lymphoid tissue; sIg = surface immunoglobulin; SLL = small lymphocytic lymphoma; TdT = terminal deoxynucleotidyl transferase.

* A number of prognostic cytogenetic abnormalities have been identified (see Chapter 22).

† A number of partner chromosomes described.

‡ Exclusively in GCB-like DLBCL.

§ Exclusively in ABC-like DLBCL.

T-cell development and biology of the T-cell lymphomas

In contrast to B-cell development, T-cell progenitors derived from common lymphoid progenitors exit the marrow and develop in the thymus. Similar to B cells, each T cell recognizes a specific antigen, but through a T-cell receptor (TCR) rather than BCR. Similar to BCRs, diversity of TCRs is generated through recombination of *V*, *D*, and *J* gene segments of the four TCR genes, *alpha* (α), *beta* (β), *gamma* (γ) and *delta* (δ). Mature T-cells express either αβ TCR or γδ TCR. Of note, αβ TCRs can only recognize antigen presented in the context of major histocompatibility complex (MHC) while γδ TCRs do not have this restriction. As such, NK-cells and γδ T-cells, which express γδ TCR, do not require antigen sensitization to become active and operate as part of our innate, rather than adaptive, immune system. Meanwhile, as developing T-cells that express αβ TCR mature in the thymus, their αβ TCR is complexed with surface CD3 and either CD4 or CD8, which identifies helper and cytotoxic T-cell subsets, respectively (Figure 21-2).

The cell of origin approach that was so effective for categorization of B-cell lymphomas has been more difficult to apply to T-cell lymphomas, due to a combination of factors including the complexity of mature T- and NK-cell lineages, with numerous functional subsets demonstrating marked phenotypic and morphologic diversity compounded by evidence of plasticity. In addition, with the noticeable exception of ALK-positive anaplastic large cell lymphoma (ALCL), few recurrent cytogenetic abnormalities have been associated with mature T-cell lymphomas and accordingly, contribute little to their categorization. Instead, clinical features and

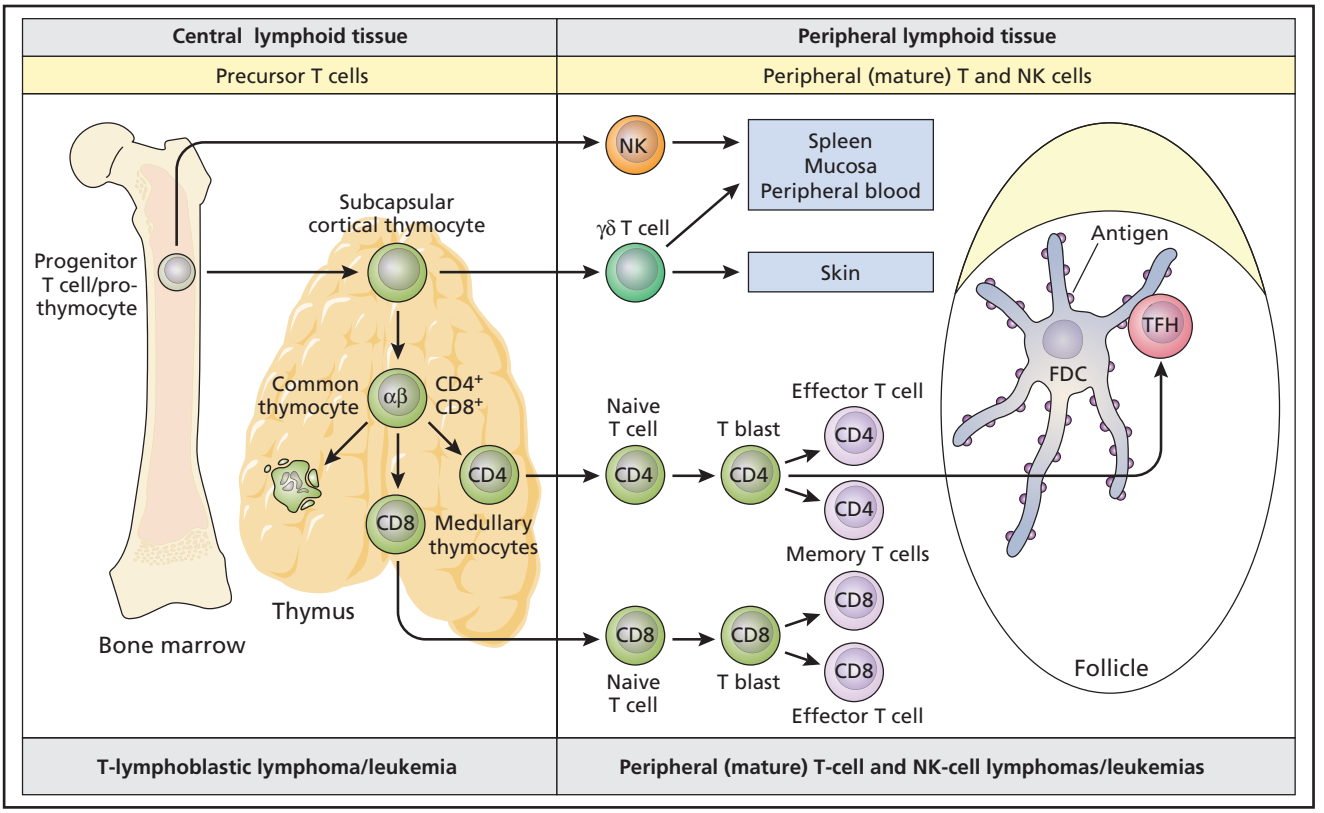

Figure 21-2 Schematic representation of T-cell differentiation (WHO 2008). FDC = follicular dendritic cells; NK = natural killer; TFH = T-helper follicular cells. Reproduced with permission from Harald Stein.

anatomic location of the disease have played a major role in defining many of the mature T- and NK-cell neoplasms included in the World Health Organization (WHO) classification, which can be grouped according to their presentation as disseminated (leukemic), predominantly extranodal or cutaneous, or predominantly nodal disease (Table 21-3).

Diagnostic testing in lymphoproliferative disorders

Diagnosis of lymphoproliferative disorders requires some expertise and relies on a combination of morphologic findings (peripheral blood, bone marrow, or lymph node), immunophenotyping, cytogenetics, and molecular genetics.

Morphology

Well-stained peripheral blood and bone marrow aspirate smears provide excellent cytologic detail, facilitating evaluation of nuclear chromatin patterns and cytoplasmic coloration as well as revealing the presence of cytoplasmic inclusions and vacuoles in lymphoid cells. The degree of nuclear chromatin condensation is helpful in differentiating lymphoid blasts, which have finely granular or "open" chromatin, from mature lymphocytes, which have more opaque and condensed chromatin. Some lymphoid malignancies, such as chronic lymphocytic leukemia (CLL), have characteristic patterns of chromatin condensation, with CLL lymphocytes typically showing a "soccer-ball" nuclear pattern. Likewise, Burkitt lymphoma cells can be recognized on smear preparations by their finely granular chromatin and strikingly blue, vacuolated cytoplasm.

Lymph node biopsies and bone marrow core biopsies lack the cytologic detail of smear preparations because tissue specimens must be fixed in formalin and dehydrated, a process that shrinks the cells and obscures cytologic detail. The benefit of tissue specimens is that they provide a glimpse of the underlying architecture, a critical component in differentiating between benign from malignant lymphoid proliferations and in the classification of lymphoid malignancies. Lymphoid malignancies typically obliterate and "efface" underlying normal architectural features and the pattern of malignant growth, for example nodular versus diffuse, guides subsequent classification. These patterns can be difficult to recognize in small biopsy specimens and accordingly, needle core biopsies of suspected lymphoid malignancies can be extremely challenging for pathologists to interpret.

Table 21-3 2008 World Health Organization classification of B-cell and T-cell neoplasms

B-cell neoplasms	T-cell neoplasms
Precursor B-cell neoplasms*	**Precursor T-cell neoplasms***
B-lymphoblastic leukemia/lymphoma NOS	T-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities	
Mature B-cell neoplasms	**Mature T-cell neoplasms**
Aggressive lymphomas	*Leukemic or disseminated*
Diffuse large B-cell lymphoma: variants, subgroups, and subtypes/entities	T-cell large granular lymphocytic leukemia†
Diffuse large B-cell lymphoma, NOS	Chronic lymphoproliferative disorders of NK cells†
Common morphologic variants: centroblastic, immunoblastic, anaplastic	T-cell prolymphocytic leukemia
Rare morphologic variants	Aggressive NK-cell leukemia
Molecular subgroups: germinal center B-cell like (GCB) and activated B-cell like (ABC)	Adult T-cell leukemia/lymphoma
Immunohistochemical subgroups: $CD5^+$ DLBCL, GCB, and non-GCB	Systemic EBV-positive T-cell lymphoproliferative disorders of childhood
Diffuse large B-cell lymphoma subtypes	
T-cell/histiocyte-rich large B-cell lymphoma	*Extranodal*
Primary DLBCL of the CNS	Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous DLBCL, leg type	Enteropathy-type T-cell lymphoma
EBV-positive DLBCL of the elderly	Hepatosplenic T-cell lymphoma
Other lymphomas of large B cells	
Primary mediastinal large B-cell lymphoma	*Cutaneous*
Intravascular large B-cell lymphoma	Mycosis fungoides†
DLBCL associated with chronic inflammation	Sézary syndrome†
Immunodeficiency-associated lymphoma	Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorder†
Lymphomatoid granulomatosis	Primary cutaneous $CD4^+$ small/medium T-cell lymphoma†
ALK-positive large B-cell lymphoma	Primary cutaneous anaplastic large cell lymphoma
Plasmablastic lymphoma	Lymphomatoid papulosis
Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease	Subcutaneous panniculitis-like T-cell lymphoma
Primary effusion lymphoma	Primary cutaneous $\gamma\delta$ T-cell lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma	Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	Hydroa vacciniforme-like lymphoma
Burkitt lymphoma	*Nodal*
Mantle cell lymphoma	Peripheral T-cell lymphoma, NOS
	Angioimmunoblastic T-cell lymphoma
Indolent lymphomas	Anaplastic large-cell lymphoma, ALK positive
Follicular lymphoma	Anaplastic large-cell lymphoma, ALK negative
Primary cutaneous follicle center lymphoma	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)	
Nodal marginal zone lymphoma	
Splenic marginal zone lymphoma	
Splenic B-cell lymphoma/leukemia, unclassifiable	
Lymphoplasmacytic lymphoma	
Heavy chain disease	
Plasma cell neoplasms	
CLL/SLL	
B-cell prolymphocytic leukemia	
Hairy cell leukemia	

CLL = chronic lymphocytic leukemia; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; HHV-8 = human herpesvirus 8; NK = natural killer; NOS = not otherwise specified; SLL = small lymphocytic lymphoma.

* All precursor neoplasms are considered aggressive.

† Indolent T-cell neoplasms, all other T-cell neoplasms are considered aggressive.

Immunophenotyping

Immunophenotyping can be performed by flow cytometry on live cells from either liquid specimens or disaggregated tissue. For fixed specimens, immunophenotyping is typically performed by 3,3'-diaminobenzidine (DAB) staining of tissue on glass slides. Immunophenotyping complements morphologic assessment by illuminating details of cell biology that would be otherwise imperceptible through the microscope. By determining cell lineage, maturation stage, and the presence of any aberrant antigen expression, immunophenotyping findings can be combined with morphologic findings to arrive at a diagnosis. For example, mantle cell lymphoma (MCL) is characterized by effacement of normal nodal architecture by small nongerminal center (CD10 negative) B-cells (CD20 positive), with aberrant coexpression of CD5 (typically a T-cell marker, but expressed on a subset of B cells) and cyclin D1 (a protein that is not expressed in normal lymphocytes; its expression results from the translocation that underlies MCL). Other characteristic immunophenotypic profiles of lymphoid malignancies can be found on Table 21-2.

For B-cell malignancies, clonality can also be identified by light-chain restriction of the surface immunoglobulin. B-cells normally express κ and λ light chains in a ratio of 2:1. A clonal expansion can be identified by a marked predominance of either κ- or λ-expressing B cells that would not be expected in a reactive process. The immunophenotyping of T-cell neoplasms is less conclusive than for B-cell disorders because T-cells lack the equivalent of light-chain restriction. Several findings can be suggestive of neoplasia, including expression of CD4 or CD8 on the majority of the T-cells, lack of expression of CD4/CD8 on the majority of T cells, or coexpression of CD4 and CD8 on the majority of T-cells. Often, however, molecular techniques to look at TCR gene rearrangements are necessary to differentiate reactive from clonal T-cell processes.

Molecular genetics and cytogenetics

Molecular genetic techniques can be helpful in assessing clonality when morphology and immunophenotyping are inconclusive. These involve isolating the DNA from a sample and subjecting it to polymerase chain reaction (PCR) to detect rearrangements of immunoglobulin or TCR genes. The demonstration of a dominant rearrangement of the immunoglobulin or TCR genes is indicative of a clonal process.

Chromosomal translocations are common in lymphoproliferative disorders and may contribute to the transformation process or cellular proliferation (Table 21-2). Commercial probes are available for detection of most translocations by fluorescent in-situ hybridization (FISH) and can be useful markers of malignancy and for identifying specific lymphoma subtypes. Use of microarray technology has defined gene expression profiles of various lymphoid malignancies and compared them to normal lymphoid populations. This technique has been successfully applied to a number of B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL), FL, CLL, and MCL to identify expression patterns that correlate with patient outcome. However, technical difficulty with assessing gene expression profiles in the clinical laboratory, especially in formalin-fixed tissues, has hampered clinical application of these findings. Despite this, pathologists and oncologists have managed to apply the DLBCL gene expression discoveries to the clinical realm by utilizing surrogate immunohistochemistry based expression panels to differentiate the better-prognosis germinal center B-cell-like DLBCL from the poor-prognosis activated B-cell-like DLBCL. More recently, next-generation sequencing (NGS) technology has been utilized to deeply interrogate the genomes of various lymphoid malignancies. While many such studies are still ongoing, landmark discoveries of single causative mutations of *BRAF* V600E in hairy cell leukemia (HCL) and *MYD88* L265P in Waldenström macroglobulinemia have thus far been reported (Table 21-2).

Classification of non-Hodgkin lymphomas

The classification of lymphoproliferative disorders continues to evolve as our understanding of the biology of these diseases progresses. The current classification system used is the *World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues*, which was updated in 2008 (Table 21-3) (Swerdlow et al., 2008) and will be updated again in 2016-2017. The B- and T-cell neoplasms are separated into precursor (lymphoblastic) neoplasms and mature B- or T-cell neoplasms. Overall, ~90% of all non-Hodgkin lymphomas (NHLs) in Western countries are of mature B-cell origin, with DLBCL and FL being the most common subtypes. In children, Hodgkin lymphoma (HL) is more predominant, and the aggressive NHLs of lymphoblastic lymphoma and Burkitt lymphoma (BL) are much more commonly encountered than indolent neoplasms. The incidence of NHL is lower among Asian populations, in whom T-/NK-cell neoplasms are more frequent.

While the premise of the WHO classification is to separate lymphoid malignancies into distinct, nonoverlapping entities, it also recognizes that the biology of particular tumors cross the boundaries between current categories. These gray zone malignancies are recognized as B-cell lymphoma, unclassifiable, with features intermediate between (i) DLBCL and classical Hodgkin lymphoma (cHL) and (ii) DLBCL and Burkitt lymphoma. Common gene expression and epigenetic profiles between primary mediastinal large B-cell

lymphoma and cHL indicate a true biologic grey zone between these two entities exists. Likewise, certain cases of DLBCL have been found to have expression profiles of Burkitt lymphoma, although they differed clinically and genetically from classic Burkitt lymphoma and vice versa. Biologically, many of these cases may lie in the gray zone because they have rearrangements in both *BCL2* and *cMYC* genes ("double-hit" lymphomas) and are more clinically aggressive than standard DLBCLs.

For clinical purposes, the NHLs can be broadly separated into indolent or aggressive categories (Table 21-3). *Indolent lymphomas* generally are incurable with most standard therapeutic approaches and are typified by a chronic course with repeated relapses and progression with standard therapy. Some of these patients, however, survive many years with remarkably stable disease even in the absence of specific therapy. Median survival is usually 8-10 years but not uncommonly may exceed 15-20 years. Most, but not all, *aggressive lymphomas* are potentially curable with combination chemotherapy. Aggressive subtypes usually have a more acute presentation often with B-symptoms and a more rapid progression than the indolent entities. In the event of failure to achieve complete remission (CR) following treatment or with relapse after an initial therapeutic response, survival usually is measured in months rather than years. Some of these patients, however, are cured by second-line chemotherapy and stem cell transplantation approaches, as described later in this chapter.

Epidemiology, pathogenesis, and molecular characterization

Data from cancer registries show that the incidence of NHL has been increasing steadily in North America and other industrial countries with a doubling of cases between 1970 and 1990 and stabilization thereafter. In 2015, there will be an estimated 71,850 new cases of NHL, representing 4.3% of all cancer diagnoses and 3.4% of all cancer deaths. The reasons for this increasing incidence are unknown but are the subject of ongoing epidemiologic investigations. Associations have been made with occupational exposure to certain pesticides and herbicides (Table 21-1). Agricultural workers with cutaneous exposure to these agents have an approximately two- to six fold increased incidence of NHL, possibly contributing to the relatively greater frequency of lymphoma in rural versus urban populations. Risks may differ between B- and T-cell lymphoma. A large epidemiologic study from the International Lymphoma Epidemiology Consortium (InterLymph) identified eczema, T-cell activating autoimmune diseases, a family history of myeloma, and occupation as a painter as increasing the risk for T-cell lymphoma. A history of B-cell-activating autoimmune disease and hepatitis C seropositivity were associated with increased risk for certain B-cell lymphomas (Morton et al., 2014).

Immunosuppression associated with HIV infection or iatrogenically induced immune suppression in the organ transplantation setting is associated with an increased incidence of aggressive B-cell lymphomas, likely due to dysregulated B-cell proliferation and susceptibility to viruses such as Epstein-Barr virus (EBV) (Table 21-1). In children, the incidence of NHL is increased in several disorders that have in common immunodeficiency from primary immune disorders, including ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable or severe combined immunodeficiency, and X-linked lymphoproliferative disorder.

Infection with the bacterium *Helicobacter pylori* is strongly associated with gastric MALT lymphoma (Table 21-1). Patients with MALT limited to the stomach often achieve CR following successful therapy to eradicate *H pylori*, indicating that the lymphoma remains dependent in part on continued antigenic drive from the microorganism. Associations have also been made between orbital infection by *Chlamydophila psittaci* and orbital adnexal MALT lymphoma, infection with *Campylobacter jejuni* and immunoproliferative small intestinal disease, and *Borrelia burgdorferi* and cutaneous MALT lymphoma. These intriguing associations need to be firmly established by additional investigation, with variable responses observed with antimicrobial agents.

Certain viral infections have been linked with specific subtypes of NHL. EBV has a clear pathogenic role in endemic as well as some cases of sporadic BL and in many cases of HIV-related aggressive B-cell lymphoma. EBV positive DLBCL of the elderly is thought to be associated with age related immunosuppression. EBV is strongly associated with extranodal T-/NK-cell lymphoma, nasal type, which is seen most commonly in Asia and in Central and South America. It is also detected in 70%-80% of cases of angioimmunoblastic T-cell lymphoma (AITL). The gamma herpesvirus human herpesvirus 8 (HHV-8, also called Kaposi sarcoma–associated herpesvirus [KSHV]), first described in Kaposi sarcoma but also associated with an unusual primary body cavity lymphoma (primary effusion lymphoma), is most commonly seen in patients with AIDS. HHV-8 also has been described in association with multicentric Castleman disease. The retrovirus human T-cell lymphotropic virus 1 (HTLV-1) is associated with adult T-cell leukemia/lymphoma endemic to Japan, central Africa, and the Caribbean. Chronic hepatitis C virus infection has been linked to the development of B-cell NHL, particularly marginal zone lymphoma and DLBCL, possibly via chronic BCR stimulation through direct binding of a viral envelope protein.

Specific chromosomal translocations are strongly associated with individual subtypes of B-cell NHL (Table 21-2). The majority of these arise early in B-cell differentiation,

during the process of immunoglobulin gene rearrangement, when errant fusion of immunoglobulin promoter and enhancer elements with other genes leads to dysregulated oncogene expression. Careful study of such translocations has provided important insights into pathogenic mechanisms in lymphoma. The most frequent of these translocations are: (i) t(14;18), with resultant overexpression of the anti-apoptotic gene *BCL2*, which is present in ~85% of FLs; (ii) t(11;14) with cyclin D1 overexpression, which is present in virtually all MCLs; and (iii) t(8;14), t(2;8), and t(8;22) of BL, which fuse an immunoglobulin heavy- or light-chain gene promoter to the *cMYC* transcription factor. *BCL6*, a chromosome 3 transcription factor gene capable of promiscuous rearrangement with multiple translocation partners, is most commonly identified in DLBCL. The t(2;5)(p23;q35) fuses the *ALK* gene with nucleophosmin and is found in a subset of CD30-positive ALCL. Several other translocation partners with the *ALK* gene also have been described in this disease. This translocation and *ALK* expression are associated with a more favorable prognosis in ALCL (see also the section "Peripheral T-cell lymphomas" in this chapter). ALK^+ lymphoma can be found in the breast in association with certain types of breast implants.

Gene expression profiling has defined molecular signatures in lymphoma that have been utilized to identify prognostically significant disease subsets in DLBCL, FL, MCL, CLL, and T-cell ALCL as well as illuminating the existence of gray zone lymphomas that lie between DLBCL and Burkitt lymphoma as well as DLBCL and cHL. More recently, next-generation sequencing has provided some early insight into the mutational landscape of several lymphomas including the previously mentioned single causative mutations of *BRAF* V600E in HCL and *MYD88* L265P in Waldenstrom macroglobulinemia. Additionally, the mutational landscape of GCB-like DLBCL has been found to be distinct from ABC-like DLBCL, with GCB-like DLBCL harboring an activating *EZH2* mutation while ABC-like DLBCL harbors activating *MYD88* mutations similar to Waldenström macroglobulinemia. These discoveries continue to refine lymphoma classification and elucidate novel therapeutic targets.

Staging and prognostic factors

Staging procedures generally include careful physical examination for lymphadenopathy and organomegaly; computed tomography (CT) scans of the neck, chest, abdomen, and pelvis; fluorodeoxyglucose positron emission tomography (FDG-PET) imaging; and bone marrow biopsy. CT or magnetic resonance imaging (MRI) of the brain and evaluation of the cerebrospinal fluid are indicated in patients with Burkitt or lymphoblastic lymphomas and also should be considered in patients with aggressive histology lymphoma involving high-risk sites, including the sinuses or testis. The Ann Arbor staging system, identifying patients as having stage I (localized) to stage IV (extensive) disease, originally was devised for use in HL but was later adopted for use in NHL. Patients are further stratified as to the absence (A) or presence (B) of symptoms, namely, fevers, drenching night sweats, or weight loss of 10% or more within 6 months of diagnosis. Several limitations become apparent when the Ann Arbor classification is applied to NHL and as a result, a revised staging system, called the Lugano classification, was proposed in 2014 (Table 21-4). Patients with Ann Arbor stage I or II disease can be grouped and considered as having "limited stage" disease while patients with Ann Arbor stage III or IV disease can be grouped in considered as having "advanced stage" disease. Other recommendations from the Lugano classification include the following: (i) FDG-PET/CT be considered standard imaging for FDG avid lymphomas while CT is indicated for non-avid histologies; (ii) reserving the suffix A or B only for HL; (iii) eliminating the X designation for bulky disease (since there is no universal definition for bulk) and replacing it with a recording of the largest nodal diameter; and (iv) elimination of the need for staging bone marrow biopsies in HL if a PET-CT was used for staging.

Lymphoma staging has only limited prognostic usefulness. To more fully incorporate additional relevant prognostic features, models have been developed in the most common NHLs, DLBCL and FL, and, more recently, MCL. The most widely used clinical prognostic model to stratify patients with aggressive NHLs is the International Prognostic

Table 21-4 Lugano staging system for NHL

Stage			
Lugano	**Ann Arbor**	**Involvement**	**Extranodal (E) Status**
Limited	I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Limited	II	Two or more lymph node regions on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Advanced	III	Involvement of lymph node regions on both sides of the diaphragm, nodes above the diaphragm with or spleen involvement	Not applicable
Advanced	IV	Additional noncontiguous extralymphatic involvement	Not applicable

Table 21-5 The IPI in DLBCL in the rituximab era

Risk group	Risk factors (no.)*	Distribution of cases (%)		4 year PFS (%)		4-year OS (%)	
		BCCA n = 365	DSHNHL n = 1062	BCCA	DSHNHL†	BCCA	DSHNHL†
Low (L)	0, 1	28%	52%	85%	87%	82%	91%
Low-intermediate (LI)	2	27%	21%	80%	75%	81%	81%
High-intermediate (HI)	3	21%	17%	57%	59%	49%	65%
High (H)	4, 5	24%	10%	51%	56%	59%	59%

Estimates are rounded off.

BCCA = British Columbia Cancer Agency; DLBCL = diffuse large B-cell lymphoma; DSHNHL = German High-Grade Non-Hodgkin Lymphoma Study Group; OS = overall survival; PFS = progression-free survival.

*IPI risk factors are age ≥60 years, abnormal LDH, PS ≥2, stage III or IV, and >1 extranodal sites.

†3-year PFS and OS.

Index (IPI; Shipp et al., 1993). The purpose was to identify pretreatment variables that predict relapse-free and overall survival (OS) in patients treated with doxorubicin-containing combination chemotherapy. The following five risk factors were found to be independently associated with clinical outcome and often are referred to by the mnemonic *APLES*: (i) age >60 years, (ii) PS >2, (iii) elevated serum lactate dehydrogenase (LDH), (iv) number of extranodal sites of disease >1, and (v) stage III or IV. The IPI score is derived as a simple additive score from 0-5 and has been widely adopted to estimate prognosis in patients with NHL and is useful in some of the other lymphoma subtypes. Of note, these survival estimates established before the use of rituximab diffuse large B-cell lymphoma.

Limited studies support that the IPI is still prognostic in the rituximab treatment era (Table 21-5). A revised IPI (R-IPI) may define new risk groups in rituximab-treated patients: very good risk (0 risk factors, 4-year PFS 90%); good risk (1, 2 risk factors, 4-year PFS 70%); and poor risk (>3 risk factors, 4-year PFS 50%). The DSHNHL group also evaluated the usefulness of the IPI in patients enrolled on prospective clinical trials, with a predominance of low-risk patients, and found that it did effectively separate patients into the previously established risk categories, although the difference between the high-intermediate and high-risk groups was small (Ziepert et al., 2010) (Table 21-5).

Although the IPI scoring system provides useful prognostic information, there is no definitive evidence that outcome is altered by using intensive regimens in high-risk patients. Numerous studies have been reported, and others are still in progress, assessing the utility of the IPI and "risk-adjusted" or "risk-adapted" therapeutic strategies. These include trials of high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) for aggressive lymphoma patients with high IPI scores; however, such strategies currently are not established as standard approaches and remain experimental (see the section "Diffuse large B-cell lymphoma" later in this chapter.). The IPI is useful in comparing studies and also in the investigation of new prognostic factors to determine the independent effect on outcome.

The IPI score is predictive of survival in indolent lymphomas, namely, FL, although using the IPI, the majority of these patients fall into the low-risk or low-intermediate-risk categories. As such, a new index was developed specifically for FL called the *Follicular-Lymphoma International Prognostic Index* (FLIPI) in hopes of better stratifying patients (Table 21-6). This index can be remembered by the mnemonic *No-LASH*. The five clinical factors that are the strongest predictors of outcome in multivariate analysis were: (i) number (no.) of nodal sites of disease (>4), (ii) elevated LDH, (iii) age >60 years, (iv) stage III or IV disease, and (v) hemoglobin <12 g/L. Compared with the IPI, the FLIPI provides a better distribution of patients across the risk categories of low risk (0 to 1 factor), intermediate risk (2 factors), or high risk (>3 factors). The 10-year OS rates were 71% (low risk), 51% (intermediate risk), and 36% (high risk), respectively (Table 21-6). Similarly, an international prognostic index for MCL (the Mantle Cell Lymphoma International Prognostic Index [MIPI]) also has been developed, incorporating age, performance status (PS), LDH, and white blood cell (WBC) level (Table 21-7).

Table 21-6 Follicular Lymphoma International Prognostic Index (FLIPI)

Risk model and group	No. of factors	Distribution of cases (%)	5-year OS (%)	10-year OS (%)
FLIPI*				
Low	0-1	36	91	71
Intermediate	2	37	78	51
High	≥3	27	53	36

*FLIPI risk factors: No-Lash = number of nodal sites of disease (>4); elevated LDH, age >60 years, stage III or IV disease, and hemoglobin ≤12 g/L.

Table 21-7 The Mantle Cell Lymphoma International Prognostic Index (MIPI)

Points	Age, Years	ECOG PS	LDH/ULN	WBC, cells/mm^3
0	<50	0-1	≤0.67	<6,700
1	50-59	—	0.67-0.99	6,700-9,999
2	60-69	2-4	1.00-1.49	10,000-14,999
3	≥70	—	≥1.50	≥5000

MIPI risk factors are age, PS, LDH, WBC level.
Formula for MIPI: [0.03535 × age (years)] + 0.6978 (if ECOG >1) + [1.367 × log10(LDH/ULN)] + [log10(WBC count)].
Simplified MIPI: low risk = 0-3 points; intermediate risk = 4-5 points; high risk = 6-11 points.
ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = [lactate] dehydrogenase; PS = performance status; ULN = upper limit of normal; WBC = white blood cell.

Role of FDG-PET imaging

FDG-PET scanning is useful both for staging and assessing response to lymphoma therapy and is generally recommended as part of routine staging and end-of-treatment response assessment in FDG-avid lymphomas. The 5-point scale (Deauville criteria, Table 21-8) should be used for PET interpretation and scores of 1-3 at completion of therapy are considered consistent with complete remission, regardless of the size of any residual masses. Some studies indicate that interim PET scanning, performed midtreatment, can identify patients at higher risk for treatment failure; however, it is unknown whether therapy should be altered based upon the results of a midtreatment PET scan. False-positive results can occur in the setting of inflammation, granulomatous disease, and infection, and a biopsy should be performed in a PET-positive patient in a remission by CT scan if high-dose chemotherapy and stem cell transplant (HDC/SCT) are under consideration.

Patient management and follow-up

With over 60 lymphoma subtypes, detailed management guidelines for each subtype and disease stage are beyond the scope of this chapter. The reader is encouraged to refer to the NCCN guidelines at http://www.nccn.org/about/nhl.pdf, which is an outstanding resource for the treating clinician.

Patient surveillance following treatment of lymphoma should address both long-term complications of therapy and disease recurrence. Long-term effects of therapy depend on the type of treatment and whether radiotherapy was also administered. For example, radiotherapy to the head and neck region leads to decreased salivation with dental caries, and if the thyroid was included in the radiation field, a large proportion of patients eventually may become hypothyroid. Thyroid-stimulating hormone (TSH) level should monitored with each follow-up visit. Hypothyroidism may raise the LDH and prompt a fruitless search for disease recurrence. Women who have had mantle radiation should receive a mammogram 10 years after radiation or at age 40 years. In younger women, MRI breast imaging also can be considered given reduced sensitivity of mammogram.

Long-term survivors are at risk of second malignancies, which is dependent on the treatment administered. For example, radiated patients are at risk for carcinomas and sarcomas in the radiated field, while those who have had alkylating agents are at risk for therapy-related myelodysplastic syndrome or acute myeloid leukemia. Once primary therapy has been completed and remission documented, patients typically are followed every 3 months for the first 2 years, then every 6 months until 5 years, and then annually thereafter.

Most recurrences of aggressive lymphoma occur in the first 2 years after treatment, although late relapses beyond 5 years do occur in a small minority of patients. Patients with indolent lymphoma have a lifelong risk of relapse and typically are seen every 3 months for the first 2 years and then every 6-12 months indefinitely. There is no evidence that routine CT or PET imaging affects outcome of patients, and newer guidelines recommend minimizing surveillance imaging in indolent lymphomas and discourage any surveillance imaging in aggressive lymphoma.

Table 21-8 Deauville 5-point scale for PET interpretation in lymphoma

Score	Visual description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Update moderately higher than liver
5	Update markedly higher than liver

Key points

- NHLs are biologically and clinically heterogeneous; accurate diagnosis by a hematopathologist using the WHO classification is essential for optimal management.
- The majority of NHLs are of B-cell origin and are categorized broadly as indolent versus aggressive subtypes.
- The incidence of NHL is increasing in Western countries.
- Specific chromosomal translocations are associated with specific subtypes of lymphoma and are pathogenetically involved in malignant transformation and progression.
- The IPI score provides important prognostic information for outcome and survival in aggressive lymphomas. The FLIPI has been developed specifically for FL.

Indolent B-cell NHL

The indolent B-cell lymphomas include the cell types shown in Table 21-3, and the most commonly encountered subtype is FL, which accounts for 20%-30% of all lymphomas. Other subtypes include marginal zone lymphomas (nodal, splenic, and extranodal [MALT] types) and lymphoplasmacytic lymphoma. This category also includes CLL/SLL, which is discussed in Chapter 22.

Clinical case

A 53-year-old man is diagnosed with stage IV FL after noticing a lump on his neck while shaving. A biopsy reveals a lymph node with enlarged, closely packed follicles with distorted architecture. Inside the follicles are small lymphocytes with irregular nuclei. The cells stain positive for CD20 and CD10. The staging evaluation reveals widespread lymphadenopathy, involving five nodal groups, with the largest node measuring just over 3 cm and 10% marrow involvement. The hemoglobin and LDH are normal. He has no disease-related symptoms and his Eastern Cooperative Oncology Group (ECOG) PS is 0. The FLIPI score is 2 and he has low tumor burden by Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.

Follicular lymphoma

FL is the prototypical and most common indolent lymphoma, with about 15,000 new cases diagnosed each year in the United States. Although incurable, the prognosis is relatively good (median OS >10 years) and appears to be improving in the immunochemotherapy era.

FLs are derived from GCB and are graded based on the number of centroblasts per high-power field: grade 1 (0-5), grade 2 (6-15), and grade 3 (>15). Grade 3 is further classified into Grade 3A (centrocytes present) and grade 3B (solid sheets of centroblasts). For purposes of classification and clinical management, grades 1 and 2 can be considered one entity, and the WHO classification uses the term *grade 1-2*. Grade 3 FL is relatively uncommon (<20% of all FLs), and the natural history of this entity is less clear. Most contemporary clinical trials will allow grade 3A to be included with grade 1-2 cases, whereas grade 3B is excluded. It is believed that grade 3B is best managed like DLBCL, but whether or not it is curable remains unclear. Immunophenotypically, FL cells are CD20+, CD10+, BCL6+, BCL2+, and CD5-. Up to 90% of cases have a t(14;18) with a higher frequency observed in grade 1-2 FLs.

In the 2008 WHO classification, there are a number of identified variants of FL. These include primary intestinal FL, extranodal FLs, and pediatric FL. Primary cutaneous follicular center lymphoma, a provisional entity in the updated WHO classification, should be distinguished from FL. It is derived from follicle center cells and can have a follicular, follicular and diffuse, or diffuse growth pattern. Unlike nodal FL, the neoplastic cells are usually BCL-2 negative. It typically occurs as solitary or localized skin lesions on the scalp, forehead, or trunk, and only 15% present with multifocal lesions. The clinical course is usually very indolent and can be managed with low-dose radiation and other site directed approaches.

Gene expression profiling has been explored in FL. In the largest study, molecular signatures divided patients into four quartiles with widely disparate median survival times (3.9, 10.8, 11.1, and 13.6 years; Dave et al., 2004). Interestingly, the signatures largely consisted of nonmalignant cells from the microenvironment. One signature was termed *immune response-1* and was associated with a more favorable prognosis and had high expression of genes expressed in T-cells. In contrast, *immune response-2* had high expression of genes expressed in monocytes or dendritic cells. Whether these signatures can be used to develop targeted therapies or are still relevant in rituximab-treated patients is unknown.

Management of localized follicular lymphoma

Limited-stage (Ann Arbor I or II) FL is relatively uncommon and as a result, there are no randomized studies indicating the optimal management strategy. Rather, most of the data are observational, derived from single-institution databases. Older studies suggested a proportion of patients might be cured with an external beam radiation. MacManus and Hoppe (1996) found that ~40% of limited-stage patients with FL remained disease free at 10 years after radiation treatment; late relapses beyond 10 years were unusual. Other studies also reported a 10-year disease-free survival (DFS) rate of ~40%-50%, suggesting that cure is possible in a proportion of patients with this approach (Wilder et al., 2001). Given the excellent long-term outcomes for patients with localized FL, there is concern for late-onset radiation-induced complications, including second primary cancers. Recent data indicate that radiation fields can be reduced without adversely impacting disease control (Campbell et al., 2011). As a result, contemporary strategies tend to utilize an involved field approach. Studies evaluating chemotherapy plus radiation (combined modality therapy [CMT]) have demonstrated improved progression-free survival (PFS) without an obvious effect on OS (Seymour et al., 2003). Therefore, the CMT approach is likely best reserved for the rare patient who presents with bulky (node >5 cm) limited stage FL. Finally, an alternative management strategy for this patient population is watch and wait. A Stanford report of stage I and II patients, who received no initial therapy, showed that more than half of the 43 patients did not require therapy at a median of 6 years and 85% of patients

were alive at 10 years (Advani et al., 2004). A report from a large observational database found the following treatment approaches were utilized for 471 stage I FL patients: R-chemo 28%, XRT 27%, observation 17%, CMT 13%, rituximab 12%, and other 3% (Friedberg et al., 2012). Approaches utilizing systemic therapy produced better PFS outcomes than XRT alone. There were no OS differences between any of the approaches.

Approach to patients with advanced-stage follicular lymphoma

Patients with advanced stage FL generally are considered "incurable" with standard chemotherapy. The disease generally is responsive to treatment, however, and there are numerous effective treatment options. As a result, the prognosis is excellent relative to other cancers. A typical patient will undergo a number of different treatments, often separated by several years. Advanced-stage FL can be thought of as a chronic disease that requires long-term management, and the management is largely a matter of how to sequence the different therapies.

The approach to a newly diagnosed patient needs to be individualized, factoring in the presence or absence of symptoms, the tumor burden, the patient age and comorbidities, and the goals of therapy. A 2 × 2 table can be constructed to help with the initial approach of separating patients by symptoms and tumor burden (Table 21-9). Using this approach, four patient categories are generated: (i) asymptomatic, low tumor burden; (ii) asymptomatic, high tumor burden; (iii) symptomatic, low tumor burden; and (iv) symptomatic, high tumor burden. Patients with asymptomatic, low-tumor-burden FL can be considered for watch and wait or single-agent rituximab. Patients with asymptomatic, high-tumor-burden FL generally start therapy soon after diagnosis, although selected patients may be observed initially, such as the very elderly or those who just meet the high-tumor-burden criteria (eg, three nodes in the 3-4 cm range). Patients with symptomatic, low tumor burden are uncommon and care should be taken to look for alternative causes of the patient-reported symptoms. If no alternative explanations are uncovered, then initiation of treatment is reasonable. From a decision-making standpoint, patients with symptomatic, high-tumor-burden FL are the most straightforward. They require treatment, although there is little consensus on which treatment is best.

Table 21-9 Algorithm for the approach to the newly diagnosed FL patient

	Low tumor burden	High tumor burden
Symptoms absent	Watch and wait vs single-agent rituximab	R-chemotherapy +/– MR vs watch and wait
Symptoms present	Single-agent rituximab vs R-chemotherapy	R-chemotherapy +/– MR

R = rituximab; MR = maintenance rituximab.

Management of asymptomatic, low-tumor-burden follicular lymphoma

Asymptomatic patients may be candidates for a strategy of watch and wait. To determine whether watch and wait is an option, one should make an assessment of the tumor burden. The GELF criteria (Table 21-10) are the most commonly used criteria to assess tumor burden and to assess eligibility for clinical trials. The watch-and-wait strategy was first advocated at Stanford University when two retrospective studies suggested no detriment in patient outcome. Three randomized clinical trials later confirmed the Stanford observations. Low-tumor-burden FL patients assigned to watch and wait experienced the same OS compared with patients assigned immediately to treatment. The median time to first chemotherapy in all studies was 2.3-3 years. All of these studies, however, were conducted in the prerituximab era.

To date, there are no studies comparing rituximab plus chemotherapy to watch and wait, and there is only one randomized clinical trial comparing single-agent rituximab to watch and wait in patients with previously untreated, asymptomatic, low-tumor-burden FL (Ardeshna et al., 2014). Patients were assigned to watch and wait (Arm A), rituximab at 4 weekly doses (Arm B), or rituximab at 4 weekly doses plus a single dose every 2 months for 2 years (Arm C). A significant prolongation in PFS and prolongation in the time to first chemotherapy was observed for the patients randomized to rituximab. With a median follow-up of 32 months, the proportion of patients progression free at 3 years was 33%, 60%, and 81% in Arms A, B, and C, respectively. The proportion of patients free of chemotherapy or radiation at 3 years was 48%, 80%, and 91% in Arms A, B, and C,

Table 21-10 GELF criteria for high tumor burden

Any nodal or extranodal mass >7 cm
Three or more nodal sites with diameter of >3 cm
Elevated LDH
Hb <10 g/dL, ANC <1.5×10^9/L, Plts <100×10^9
Spleen >16 cm by CT scan
Risk or organ compression or compromise
Significant serous effusions

Meeting any one criterion qualifies as high tumor burden. All must be absent to qualify as low tumor burden.
ANC = absolute neutrophil count; GELF = Groupe d'Etude des Lymphomes Folliculaires; Hb = hemoglobin; LDH = lactate dehydrogenase; Plts = platelets.

respectively. There is no difference, however, in the OS at 3 years (95% in all arms). The study also evaluated quality of life (QOL). Given that these patients are symptom free, the main QOL issues tend to be anxiety, depression, and adjustment to illness. The study found that anxiety and depression were more common in patients with low-tumor-burden FL than in the general population, but still relatively infrequent at 13% and 3%, respectively. Patients in all treatment arms adapted to their illness over time. The patients identified as "anxious" adapted more readily when assigned to rituximab treatments. The interpretation of this study vary. It is reasonable to conclude that: (i) given no OS difference observed to date, watch and wait remains a reasonable standard for the asymptomatic, low-tumor-burden FL population; (ii) some benefits are associated with immediate rituximab therapy, such as improved PFS and a longer time to first chemotherapy (these benefits should be discussed with patients); and (iii) a subset of patients (perhaps 15%) with particular difficulty adjusting to their diagnosis may experience a QOL benefit from single-agent rituximab.

If administering single-agent rituximab to a patient with low-tumor-burden FL, should one utilize a maintenance strategy or simply retreat at progression? This dosing question was addressed in the RESORT study (Kahl et al., 2014). After induction therapy with single-agent rituximab, patients with low-tumor-burden FL were randomized to receive maintenance rituximab until treatment failure or to be periodically retreated with rituximab (retreated with 4 weekly doses at each progression) until treatment failure. The trial revealed no difference in the time to treatment failure between the two dosing strategies. Patients on the maintenance arm, however, utilized four times as much rituximab. There was no difference in quality of life, depression, or anxiety between the two strategies. On the basis of these results, a re-treatment strategy is preferred if opting for single-agent rituximab in this patient population.

Therapy of symptomatic, high-tumor-burden follicular lymphoma

The addition of rituximab to conventional chemotherapy, has improved outcomes in FL, including response rates, PFS, event-free survival (EFS), and OS. Table 21-11 summarizes major studies combining rituximab with chemotherapy.

Clearly, rituximab added to chemotherapy is a therapeutic advance in FL; however, the optimal chemotherapy backbone remains unsettled. Data generated prior to the introduction of bendamustine in the US indicated the most commonly used regimens in the United States were R-CHOP (rituximab, cyclophosphamide, vincristine, prednisone) (60%), R-CVP (rituximab, cyclophosphamide, prednisone) (27%), and R-fludarabine-based (13%) (Friedberg et al., 2009). A randomized comparison of these regimens indicated R-CHOP had the best risk-benefit profile of the three, as it was more active than R-CVP and less toxic than R-FM (Federico et al., 2013).

However, bendamustine, an alkylating agent, has gained widespread adoption as the chemotherapy platform of choice in FL. A phase 3 trial comparing BR to R-CHOP demonstrated better efficacy and reduced toxicity with BR (Rummel et al., 2013). In this multicenter phase 3 study, 549 patients with high-tumor-burden indolent NHL and MCL (median age 64 years) were randomized to receive bendamustine 90 mg/m^2 on days 1 and 2, with rituximab 375 mg/m^2 on day 1, every 28 days (the BR group) or to receive standard R-CHOP chemotherapy every 21 days. The overall response rates (ORR) were similar in the BR versus R-CHOP groups (92.7% vs 91.3%, respectively), but the CR rate was significantly higher in the BR group (39.8%) compared with the R-CHOP group (30.0%) ($P = 0.03$). When evaluating just the FL patients, with a median follow-up of 45 months, the median PFS was significantly longer after BR compared with R-CHOP (median PFS, not reached vs 40.9 months, $P = 0.007$). OS did not differ between both groups. There was less hematologic toxicity, alopecia, infections, peripheral

Table 21-11 Randomized trials of chemotherapy versus R-chemotherapy in high tumor burden, advanced-stage follicular lymphoma

Study	Treatment	*N*	Median follow-up	ORR	Time to event	OS
Hiddemann, et al. *Blood*. 2005	R-CHOP vs CHOP	223 vs 205	1.5 years	96% vs 90%	88% vs 70% (2-year DoR)	95% vs 90% (2-year OS)
Marcus, et al. *J Clin Oncol*. 2008	R-CVP vs CVP	162 vs 159	4.5 years	81% vs 57%	38 months vs 14 months (median DoR)	83% vs 77% (4-year OS)
Herold, et al. *Ann Onc*. 2011	R-MCP vs MCP	181 vs 177	6 years	92% vs 75%	57% vs 25% (6-year PFS)	80% vs 65% (6-year OS)
Bachy, et al. *Ann Onc*. 2011	R-CHVP-IFN(6) vs CHVP-IFN(12)	175 vs 183	8 years	81% vs 72%	44% vs 28% (8-year EFS)	70% vs 79%* (8-year OS)

CVP = cyclophosphamide, vincristine, prednisone; DoR = duration of response; DFS = disease-free survival; EFS = event-free survival; MCP = mitoxantrone, chlorambucil, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; R-MCP = rituximab, mitoxantrone, chlorambucil, prednisone.

* *P* value not significant.

neuropathy, and stomatitis with BR. Drug-associated erythematous skin reactions were seen more frequently in the BR group. These data suggest that BR is a better option for untreated high-tumor-burden FL.

A confirmatory randomized phase 3 trial (BRIGHT study) was conducted in North America (Flinn et al., 2014). Previously untreated indolent NHL patients with high tumor burden were randomized to BR or R-CHOP/R-CVP. Control arm patients were identified as an R-CHOP or R-CVP candidate prior to randomization. The primary endpoint was to show noninferiority of BR in the CR rate. Seventy percent of the 447 enrolled patients had FL, and in these patients BR therapy was found to be noninferior to the R-CHOP/R-CVP control arm for CR rate (30% vs 25%) and the overall response rate (99% vs 94%). Time-to-event data was not reported. Side effect profiles were distinct, with more GI toxicity and rash with BR and more neuropathy and alopecia with R-CHOP/R-CVP. Although, the BRIGHT data do not exactly replicate the StIL data for BR, they do suggest that BR remains a very reasonable alternative to R-CHOP or R-CVP in FL.

The question of whether to administer maintenance rituximab after frontline R-chemotherapy was addressed in the phase 3 PRIMA trial (Salles et al., 2010). The study evaluated the efficacy and safety profile of maintenance rituximab in newly diagnosed FL patients who responded to initial treatment with rituximab plus chemotherapy. Induction treatment was selected by center; R-CHOP (75%), R-CVP (22%), or R-FCM (3%). Patients were randomized to either observation or a single dose of rituximab every 2 months for 2 years. At a median follow-up of 36 months from randomization, the 2-year PFS in the maintenance rituximab arm was 75% versus 58% in the observation arm ($P < 0.0001$). The beneficial effect of maintenance rituximab was seen irrespective of the induction chemotherapy backbone and in both CR and partial remission (PR) patients. Grade 3-4 adverse events were slightly higher in the maintenance rituximab arm (24% vs 17%). No difference in OS was observed. Given the lack of OS benefit, the decision regarding the use of maintenance rituximab can be individualized. Rituximab administration does carry low risk for neutropenia and rarely more serious toxicities such as progressive multifocal leukoencephalopathy. As maintenance, rituximab generally is well tolerated; it has become a commonly utilized strategy in the United States. Regarding the duration of maintenance rituximab, available data suggest that 2 years is safe, but data beyond 2 years is lacking.

Therapy for relapsed and refractory follicular lymphoma

Multiple options exist for the treatment of patients who have failed first-line therapy, and the decision of which therapy to use depends on a number of factors, including the prior treatment utilized, duration of prior response, patient age, comorbid illnesses, and goals of therapy. Options range from low-risk strategies, such as single-agent rituximab, to high-risk/high-reward strategies, such as allogeneic stem cell transplantation (alloSCT), with many options in between. A recent report from a large observational database reveals a substantially worse overall survival for patients who relapse within 2 years of initial therapy with R-CHOP compared to patients who remain in remission longer than 2 years (Casulo et al., 2015). These high-risk patients should be considered for more aggressive strategies (such as SCT) or investigational approaches.

Bendamustine is approved in the United States for use in patients with rituximab-refractory indolent B-cell lymphoma. A pivotal trial in 100 patients reported an ORR of 75% with a median PFS of 9.3 months (Kahl et al., 2010). The FDA-approved dose of single-agent bendamustine is 120 mg/m^2 given intravenously on days 1 and 2 of 21-day cycles. Approximately two-thirds of patients required dose modifications or delays, mainly due to cumulative myelosuppression. In addition, most practitioners prefer to administer bendamustine with rituximab. An expert panel has published guidelines on bendamustine dosing when combined with rituximab, and a recommend 90 mg/m^2 on days 1 and 2 repeated every 28 days (Cheson et al., 2010). Lower doses (such at 70 mg/m^2) may be more appropriate in the elderly.

A new option for relapsed FL is the PI3Kδ inhibitor idelalisib. Idelalisib targets the delta isoform of PI3K, an enzyme downstream from the B-cell receptor which eventually signals through AKT and mTOR. In a phase 2 study of 125 patients with indolent NHL who were considered refractory to both rituximab and an alkylating agent, idelalisib was administered at a dose of 150 mg BID until PD or patient withdrawal (Gopal et al., 2014). The response rate was 57% with a median duration of 12.5 months. Grade 3 or higher toxicities included neutropenia (27%), transaminase elevations (13%), diarrhea (13%), and pneumonia (7%). Based upon this data, idelalisib received accelerated approval by the FDA in 2014. Another option for patients who relapse after an alkylator-based therapy are fludarabine-based regimens. They should be used with caution in heavily pretreated or elderly patients, however, due to immunosuppression. Patients are at increased risk of *Pneumocystis jirovecii* and reactivation of herpes zoster. Prophylaxis with trimethoprim/sulfamethoxazole and acyclovir should be considered, particularly in elderly patients. Furthermore, if ASCT is considered as a future treatment option, the number of cycles with fludarabine should be minimized to avoid stem cell toxicity.

RIT is also a viable option for patients with indolent B-cell NHL if the bone marrow is minimally involved and the disease is not bulky. With Y90 ibritumomab tiuxetan, response rates are ~70% and response duration is, on average, 11-15 months. Single-agent rituximab can be used in relapsed lymphoma, although now that most patients have received it with their primary therapy and possibly as maintenance, more and more patients are becoming rituximab refractory. For patients who are still rituximab sensitive, it is an attractive option for elderly patients who will not tolerate cytotoxic agents well.

Stem cell transplantation

HDC with autologous stem cell transplant (ASCT) and alloSCT are both useful strategies in the management of FL, particularly for younger patients with high-risk features, such as a brief remission to previous therapy. A review of 904 patients in the International Bone Marrow Transplant Registry who underwent autologous or allogeneic transplantation for FL revealed that durable remissions could be induced with either technique (van Besien et al., 2003). A lower 5-year recurrence rate with allogeneic transplantations was offset by a higher treatment-related mortality (TRM) compared with autologous transplantation, leading to similar 5-year survival rates of 51%-62%. To reduce the TRM of alloSCT, most centers now favor a nonmyeloablative strategy in FL. Results utilizing a nonmyeloablative allogeneic SCT strategy vary widely in the literature. For example, a series of 62 patients treated at the Fred Hutchinson Cancer Center (FHCC) demonstrated a 3-year OS and PFS of 67% and 54%, respectively (Rezvani et al., 2008). Alternatively, a highly selected group ($n = 47$) treated at the M.D. Anderson Cancer Center achieved an 11-year OS and PFS of 78% and 72%, respectively (Khouri et al., 2012).

There is one small, randomized clinical trial (the CUP trial), examining ASCT versus standard therapy in patients with relapsed follicular lymphoma (Schouten et al., 2003). The study, conducted in the prerituximab era, found improved PFS and a trend toward improved OS. An interesting long-term analysis of patients receiving myeloablative chemotherapy followed by ASCT comes from investigators at St. Bartholomew's Hospital (London) and the Dana-Farber Cancer Institute (Boston) (Rohatiner et al., 2007). A cohort of 121 patients, with a median follow-up of 13.5 years, were noted to have a plateau in the remission duration curve beginning around year 8. Nearly half the patients were still in remission at 10-15 years, suggesting some patients may be cured. Results were substantially better for patients treated in second remission as opposed to later in the disease course, suggesting there may be an optimal window to consider ASCT in FL.

Marginal zone lymphomas

The WHO classification separates the marginal zone B-cell lymphomas (MZL) into extranodal MZL of MALT, nodal MZL, and splenic MZL (SMZL). The morphology of these disorders is characterized by an infiltrate of centrocyte-like small cleaved cells, monocytoid B-cells, or small lymphocytes; they may exhibit an expanded marginal zone surrounding lymphoid follicles. The immunophenotype is characterized by expression of CD20 but lack of CD5 or CD10 expression (Table 21-2); this marker profile is useful in distinguishing MZL from SLL, MCL, and FL. A feature common to many cases of MZL is association with chronic antigenic stimulation by microbial pathogens or autoantigens, as described above. Examples include gastric MALT (*H pylori*), cutaneous MALT (*B burgdorferi*), ocular adenxal MALT (*C psittaci*), nodal MZL (hepatitis C), SMZL (hepatitis C), parotid MALT (Sjögren syndrome), and thyroid MALT (Hashimoto thyroiditis). There is significant geographic variation in the association with certain microbial pathogens. For example, the prevalence of *C psittaci* in patients with ocular adnexal MALT appears to be 50%-80% in Italy, Austria, Germany, and Korea, whereas this organism is observed infrequently in Japan, China, and the United States.

MALT lymphomas

Extranodal MZLs or MALT lymphomas constitute ~70% of all MZLs. They occur in mucosal sites, predominantly gastric or intestinal, and some nonmucosal extranodal sites, including the lung, salivary gland, ocular adnexa, skin, and thyroid. These sites often are affected by chronic infection or inflammation, such as Sjögren syndrome or Hashimoto thyroiditis. The typical presentation of MALT lymphoma is an isolated mass in any of these extranodal sites or an ulcerative lesion in the stomach. Clinically, they are typically indolent lymphomas, with 10-year OS rates of 90% in many series. MALT lymphomas can be characterized as either gastric (30%-40%) or nongastric (60%-70%), and the approach to disease management is site specific. Approximately 90% of gastric MALT lymphomas are associated with *H pylori* infection. Newly diagnosed patients typically report dyspepsia, pain, reflux symptoms, or weight loss. Upper endoscopy can reveal erythema, erosions, ulcers, or masses. A consistent observation has been that 70%-80% of gastric MALT lymphomas durably regress following effective *H pylori* antibiotic therapy (Nakamura et al., 2012). The most widely used antibiotic regimen is a combination of amoxicillin, omeprazole, and clarithromycin. Metronidazole is an effective alternative antibiotic in patients with a

penicillin allergy. Lymphoma responses can be slow, taking up to 6 months to 1 year. Repeat assessment of *H pylori* either by histologic examination or a urea breath test is necessary to ensure that the bacteria have been eradicated. The strongest predictor for lymphoma nonresponse to antibiotic therapy is the presence of the t(11;18) translocation, which is present in 20%-30% of cases. In the series reported by Nakamura et al. (2012), only 3 out of 30 patients with t(11:18) experienced lymphoma regression following *H pylori* eradication therapy. In patients who do not respond to antibiotics or in *H pylori*-negative cases, involved-field radiotherapy (IFRT) has been highly effective with DFS or PFS rates of >90% at 10 years (Goda et al., 2010). The prognosis for early stage gastric MALT is excellent, with most series reporting 10-year OS rates in excess of 90%. For patients with advanced stage disease, regimens similar to those used in FL, including rituximab-based combinations, can be used. Transformation to DLBCL is possible, but a remarkable observation has been the regression of early stage *H pylori*-positive gastric diffuse large B-cell lymphomas with *H pylori* eradication therapy. This observation was noted in DLBCL clearly arising from gastric MALT (transformation) and in de novo DLBCL (no apparent underlying MALT) (Kuo et al., 2012).

Nongastric MALT lymphomas usually have an indolent course, including the one-third of patients who present with stage IV disease (Thieblemont et al., 2000). OS at 10 years exceeds 90% in many series. The most common locations are the salivary glands (26%), ocular adnexa (17%), skin (12%), lung (8%), upper airways (7%), thyroid (6%), and intestinal tract (5%) (Zucca et al., 2003). Treatment approaches depend on both stage and site of primary involvement and may include surgery, radiation therapy, or chemotherapy. Radiation therapy produces excellent results in limited-stage disease (Goda et al., 2010). Many patients can be managed with a watch-and-wait approach. Patients with advanced-stage disease typically can be managed using the same principles used for FL. Rituximab added to chemotherapy was shown to improve EFS in a RCT (Zucca et al., 2013). Recurrences tend to occur in a site-specific fashion (ie, pulmonary MALT tends to recur in the lung), and so monitoring can be primarily (although not exclusively) site directed. An emerging story is the association of *C psittaci* and ocular adenexal MALT. Several regions of Europe have reported associations in >50% of cases. A recent European multicenter phase 2 study, testing the efficacy of doxycycline, detected evidence of *C psittaci* in 39 out of 44 patients (Ferreri et al., 2012). Lymphoma regression was observed in 65% of the doxycycline-treated patients and the responses tended to be durable. Nonresponse was associated with failure to eradicate the *C psittaci* organism.

Nodal MZL

Nodal MZL, previously known as monocytoid B-cell lymphoma, also arises from marginal zone B-cells. Whenever nodal MZL is diagnosed, a careful history and physical examination should be pursued for a possible coexisting extranodal MALT lymphoma component, which may be identified in up to one-third of cases. It more commonly presents with advanced-stage than with MALT-type MZL. The t(11;18) karyotypic changes identified in MALT are absent in nodal MZL, and no specific or recurring karyotypic anomaly has been described. IgM monoclonal gammopathy can occur in ~10% of cases. HCV infection is reported in up to 25% of patients. Across reported series, the 5-year OS is 60%-70%; however, the EFS is only 30%, which likely reflects more commonly encountered advanced-stage disease. Management is similar to the approach recommended in follicular lymphoma.

In the updated WHO classification, a new category was introduced—pediatric nodal MZL—which has distinctive clinical and morphologic characteristics. There is a male predominance (20:1), and patients usually present with localized asymptomatic adenopathy in the head and neck region. Morphologically, the infiltrate is similar to that seen in adults, except that progressively transformed germinal centers often are seen.

Splenic MZL

SMZLs are uncommon. The median age at diagnosis is 68 years, and it is more common in females. Patients usually present with symptomatic splenomegaly. Generalized lymphadenopathy is uncommon, but patients may have associated splenic hilar nodal or hepatic involvement. The bone marrow and blood typically are involved and villous lymphocytes may be seen. Diagnosis usually is based on spleen histology following splenectomy or after bone marrow examination. Clinically, it can be confused with CLL, MCL, FL, HCL, or WM. Unlike CLL and MCL, it is typically CD5 negative. Unlike FL, it is CD10 negative. Unlike HCL, which is CD103 positive and replaces the splenic red pulp, SMZL is CD103 negative and replaces the splenic white pulp. There is no reliable immunophenotypic method to distinguish SMZL from WM, so morphologic and clinical features must be used. Clinically, SMZL is more likely to have significant splenomegaly, whereas WM typically has a larger monoclonal protein (Arcaini et al., 2009). A prognostic model, using hemoglobin <12 g/dL, elevated LDH, and albumin <3.5 g/dL, has identified three distinctive risk groups (Arcaini et al., 2006). OS at 5 years was 88%, 73%, and 50% for patients with 0, 1, and 2-3 risk factors, respectively. Splenectomy has long been considered the optimal first-line

therapy in symptomatic patients or in the case of cytopenias due to splenomegaly. However, single-agent rituximab has been reported to be remarkably active, with an ORR of 100% in a series of 16 patients. In an observational retrospective study, rituximab produced more durable remissions than did splenectomy (Kalpadakis et al., 2013). Regimens active in other indolent lymphomas are appropriate for patients requiring systemic therapy. Some cases have been associated with hepatitis C infection, and responses have been reported with clearance of the virus with pegylated interferon and ribavirin (Hermine et al., 2002).

Lymphoplasmacytic lymphoma and Waldenström macroglobulinemia

Lymphoplasmacytic lymphoma (LPL) is defined in the WHO classification as an indolent neoplasm of small B-lymphocytes, plasmacytoid lymphocytes, and plasma cells. The lymphoma cells may express B-cell markers CD19 and CD20 and are CD5 and CD10 negative, much like the MZLs (Table 21-3). These entities are described further in Chapter 23.

Hairy cell leukemia

Hairy cell leukemia (HCL) is an indolent B-cell lymphoproliferative disorder characterized by neoplastic lymphocytes with cytoplasmic "hairy" projections on the cell surface, a positive tartrate-resistant acid phosphatase stain, and an immunophenotype positive for surface immunoglobulin, CD19, CD20, CD22, CD11c, CD25, and CD103 (Table 21-2). Marrow biopsy demonstrates a mononuclear cell infiltrate with a "fried egg" appearance of a halo around the nuclei and increased reticulin and collagen fibrosis. Nearly 100% of cases will harbor the *BRAF* V600E mutation, abnormally activating the BRAF-MEK-ERK pathway, and BRAF inhibitors have demonstrated single agent activity in relapsed HCL (Pettirosi et al., 2015).

The typical presentation is that of a middle-age man (median age, 50-55 years) with pancytopenia, monocytopenia, splenomegaly, and an inaspirable bone marrow (dry tap). HCL is rare, representing 2% of all leukemias. Making the proper diagnosis is crucial because of its generally favorable prognosis, with a 10-year OS exceeding 90%, and its excellent treatment response to nucleoside analogs (Grever, 2010). Most patients with HCL require therapy to correct cytopenias and associated complications in addition to the presence of symptomatic splenomegaly. If a patient is asymptomatic and cytopenias are minimal, patients may be initially observed. HCL has a unique sensitivity to purine analogs. The nucleoside analogs cladribine or pentostatin are the treatments of choice in HCL in view of the high response rates and durable remissions achieved. Cladribine is used more commonly because of the short duration of therapy required, and it also is available as a subcutaneous injection. In one large series of 233 patients with long-term follow-up, the ORR and CR rate with either of these agents was 97% and 80%, respectively (Else et al., 2009). The median recurrence-free survival was 16 years, and many of the relapses were observed 5-15 years after treatment, highlighting the unique natural history of this disease. It currently is recommended that assessment of response should be determined 4-6 months following the end of treatment and if only a PR is attained then a second course can be given (Jones et al., 2012).

HCL-variant is categorized separately in the WHO classification and, despite its name, it is considered unrelated to HCL. It does not harbor the *BRAF*-V600E mutation. It differs from HCL in the lack of monocytopenia and by the presence of an elevated white blood cell count. The bone marrow is easier to aspirate as the reticulin fiber content is low. The immunophenotype of HCL-variant also differs in that the cells are CD25 negative. CD103 is expressed infrequently and CD11c is usually positive. Unlike HCL, HCL-variant responds poorly to purine analogs. Splenectomy can result in good PR in two-thirds of patients. Case reports have shown CRs after rituximab.

Transformation to aggressive lymphoma in indolent lymphomas

Histologic transformation (HT) is the development of aggressive NHL in patients with an antecedent history of indolent lymphomas. It most commonly occurs in follicular lymphoma but can occur in any of the indolent lymphomas. The British Columbia Cancer Agency reported on the incidence and outcome of 600 patients with FL who subsequently developed transformed lymphoma. Diagnoses were either made clinically (sudden increase in LDH >2× the upper limit of normal, discordant nodal growth, or unusual extranodal sites of involvement) (37%) or pathologically (63%). In this series, the annual risk of transformation was 3% per year, with a 10- and 15-year risk of 30% and 45%, respectively. Overall, the median posttransformation survival time was 1.7 years, with superior outcomes observed in limited-stage patients. Similar results were observed in a series from St. Bartholomew's, where histologic transformation was observed in 28% of patients with FL by 10 years. However, outcomes for patients with HT appear to be markedly better in the rituximab era with median OS of 50 months in one series (Link et al., 2013). FDG-PET imaging can be helpful to direct the site to biopsy when establishing HT. Histologically, DLBCL is the most frequently observed subtype. One should assay for MYC and BCL-2 by FISH and by immunohistochemistry. The treatment is directed at the

aggressive lymphoma and depends on a variety of factors, including age, comorbidities, and extent of prior treatment for the FL. Anthracyclines should be included in the treatment if not previously used and if there are no contraindications. Consideration for stem cell transplant consolidation is warranted in eligible patients (Villa et al., 2013).

Key points

- Follicular NHL is the most common indolent NHL.
- Patients with asymptomatic, advanced-stage indolent NHL may be followed without specific therapy to assess the pace of disease, or single-agent rituximab may be used to delay the use of systemic chemotherapy.
- Rituximab plus chemotherapy is recommended in patients with symptomatic disease or high tumor burden by the GELF criteria.
- Maintenance rituximab improves PFS. To date, there is no proven OS benefit.
- There are a multitude of therapeutic options for relapsed indolent lymphoma, including stem cell transplantation.

Aggressive B-cell lymphomas

The most prevalent of the aggressive lymphomas is DLBCL. Other histologies in this category include MCL, BL, lymphoblastic lymphoma, and most of the T- and NK-cell lymphomas (Table 21-3). These neoplasms are characterized by a more acute presentation and, although often curable (except for MCL), are associated with relatively short survival in the absence of therapy-induced remission. This chapter focuses on the mature B- and T-/NK-cell neoplasms.

Clinical case

A 52-year-old man is diagnosed with stage IVB DLBCL. On CT imaging, the largest nodal mass was 6 cm in the retroperitoneal region, bone marrow biopsy shows involvement with a low-grade lymphoma. Laboratory studies show a normal complete blood count (CBC), and chemistries aside from an LDH elevated 1.5 times normal. His ECOG PS is 2. Immunophenotypic stains of the lymphoma cells reveal them to express CD19, CD20, κ-light chains, BCL2, and MUM1/IRF4. They are negative for CD10 and BCL6 expression.

Diffuse large B-cell lymphoma

DLBCL is composed of large B-cells with a diffuse growth pattern. The new WHO classification recognizes several subcategories of DLBCL, including molecular subtypes (GBC and ABC; see later sections); pathologic subtypes, including T-cell-rich B-cell lymphoma; and defined disease entities, including PMBCL. Other than primary CNS lymphoma (PCNSL) treatment approaches are similar for the DLBCL subtypes.

DLBCL constitutes 25%-30% of all NHLs and can present with nodal or extranodal disease. Bone marrow involvement with large cell lymphoma occurs in fewer than 10% of cases. Another 10%-20% of patients have discordant marrow involvement with a low-grade B-cell lymphoma, despite a nodal biopsy consistent with DLBCL.

In addition to the B-cell markers CD20 and CD19, the neoplastic cells may also express CD10 (30%-60%), BCL6 (60%-90%), and IRF4/MUM1 (35%-65%). Rare cases may express CD5 (10%) and must be distinguished from the blastoid variant of MCL, which is cyclin D1 positive. As described, two molecularly distinct subtypes of DLBCL are recognized: GCB, which has a gene expression profile similar to germinal center B-cells ($CD10^+$ and $BCL6^+$); and ABC, which has a profile similar to activated peripheral B cells ($IRF4/MUM^+$) with a prominent NFkB gene signature.

Clinical prognostic factors in DLBCL

Approximately 60% of patients diagnosed with DLBCL can be cured with rituximab-based chemotherapy; however, low- and high-risk groups can be further defined by clinical and biological factors. Although the IPI is robust and relevant in the modern rituximab treatment era, it does not capture all prognostic information. Bulky disease (often defined at >10 cm, although there is not universal agreement on the definition of bulk in DLBCL) appears to increase the risk for local relapse. Particular sites of extranodal disease also are associated with prognosis. Concordant involvement of the bone marrow with DLBCL, but not discordant involvement with a low-grade lymphoma, is associated with an inferior outcome (Sehn et al., 2011). The patient described earlier has an IPI score of 3 (advanced stage, poor PS, elevated LDH), placing him in a high-intermediate risk group with an expected 5-year probability of survival with R-CHOP of 50%-60%, and the bone marrow involvement does not affect outcome because it is low-grade lymphoma. Testicular involvement with DLBCL also is associated with an aggressive course with a propensity for late relapses, CNS relapse (leptomeningeal and parenchymal), and recurrence in the contralateral testicle. Even patients with localized disease should be treated with six cycles of R-CHOP with radiotherapy to the contralateral testicle. Strong consideration also is given for CNS prophylaxis as outlined in the following section.

Biological prognostic factors in DLBCL

Although the IPI is easy to apply and remains valid in the current treatment era, it fails to capture underlying biological heterogeneity. As described above, DLBCL can be divided molecularly by GEP into the GCB and ABC subtypes, which also have a distinct signature from PMBCL. ABC DLBCL has

an inferior prognosis, independent of the IPI. Furthermore, it is clear that prognosis also is affected by the tumor microenvironment in which a signature rich in extracellular matrix and histocytes (stromal 1) is associated with a favorable prognosis and a signature rich in angiogenesis markers (stromal 2) is associated with an aggressive course (Lenz et al., 2008). The use of GEP has had limited clinical utility due to long turnaround time, the need to use fresh frozen tissue, and technical complexity.

Immunohistochemical (IHC) algorithms have been used in an attempt to capture the cell-of-origin (COO) phenotype using a methodology that can be applied routinely in clinical practice. Hans et al. (2004) first reported IHC algorithm to distinguish the GCB versus non-GCB subgroups using CD10, BCL6, and IRF4/MUM1. Using the cDNA microarray as the gold standard, the sensitivity of the IHC COO subgrouping was 71% for the GCB group and 88% for the non-GCB group. Other algorithms have been proposed that also have a lower sensitivity than gene expression profiling. These results, however, have been inconsistent as to whether the COO distinction by IHC can be applied to rituximab-treated patients. One study found that none of the applied five different IHC algorithms could distinguish COO subgroups with prognostic significance. In contrast, another study found that the Tally algorithm, which uses CD10, GCET, IRF4/MUM1, and FOXP1, showed the best concordance with microarray data and maintained prognostic significance. Given these inconsistencies and lack of data suggesting that alternate therapies may affect outcome, the COO information, whether by molecular profiling or immunohistochemistry, should not be used to direct treatment decisions outside of clinical trials.

Recent technological advances in GEP, allows real time COO determination from formalin-fixed paraffin-embedded tissue (FFPET). The Lymphoma/Leukemia Molecular Profiling Project developed Lymph2Cx assay, a parsimonious digital gene expression (NanoString)-based test for COO assignment in FFPET. A 20-gene assay was trained using 51 FFPET biopsies and the locked assay was subsequently validated using an independent cohort of 68 FFPET biopsies (Scott et al., 2014). Comparisons were made with COO assignment using the original COO model on matched frozen tissue. The assay was highly accurate, with only 1 case with definitive COO being incorrectly assigned with >95% concordance of COO assignment between two independent laboratories. The test turnaround time is several days making Lymph2Cx attractive for implementation in clinical trials and practice.

MYC is translocated in ~5%-10% of DLBCLs, and early studies have suggested that it is associated with an aggressive course in the pre- and postrituximab treatment eras (Barrans et al., 2010; Savage et al., 2009). In some cases, there is also a t(14;18) involving BCL2, the so-called double-hit lymphomas that can occur after a proceeding FL or de novo as the first manifestation of disease presentation. The combination of MYC driving cellular proliferation and BCL2 preventing apoptosis has proven to be very difficult to cure. Double-hit lymphomas (DHL) can occur with DLBCL or more commonly, B-cell lymphoma, unclassifiable with features intermediate between BL and diffuse large B-cell lymphoma (Johnson et al., 2009). The outcome is extremely poor in lymphomas with dual *BCL2* and MYC translocation B-cell lymphomas, and these patients are considered for investigational therapies. With the recent availability of a MYC antibody for IHC analysis, two large-scale studies have evaluated the prognostic importance of MYC and BCL2 protein expression (double expressers) in DLBCL patients treated with R-CHOP chemotherapy (Green et al., 2012; Johnson et al., 2012). MYC protein expression was found in approximately one-third of cases, far more than that captured by fluorescence in situ hybridization (FISH) analysis (11%) or high MYC mRNA expression, suggesting the multiple roads of *MYC* deregulation exist. Importantly, the double expressers exhibited a poor outcome (5-year OS 39% vs 70%, $P < 0.001$; Green et al., 2102: 3-year OS 43% vs 86%, $P < 0.001$; Johnson et al). The significance of this double-hit score is independent of the IPI and patients with a high IPI and dual-protein expression have an extremely aggressive course with a median PFS of only 6 months.

Treatment of newly diagnosed DLBCL

Advanced-stage DLBCL

The backbone of treatment of all subtypes of DLBCL is anthracycline-based treatment with R-CHOP chemotherapy. With this approach, ~60% of patients are cured.

Rituximab has several mechanisms of action, including the ability to sensitize otherwise-resistant lymphoma cells to chemotherapy agents in vitro, perhaps in part via downregulation of the BCL-2 protein. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) published a landmark phase 3 clinical trial in which 399 patients 60-80 years of age with previously untreated advanced-stage CD20 + DLBCL were randomized to receive CHOP for eight cycles or R-CHOP on a standard 21-day schedule. An improvement in all endpoints, including CR rate, EFS, and OS, favoring R-CHOP over CHOP was demonstrated. With longer follow-up, the results held, and R-CHOP quickly became the standard of care for advanced-stage DLBCL around the world (Coiffier et al., 2002) (Table 21-12). More recently, the outcome of patients in this study followed for a median 10 years was reported demonstrating a 10-year PFS for R-CHOP treated patients of 35% (vs 20% with CHOP alone) and 10-year OS of 43.5% (vs 27.6%) (Table 21-12). A similar phase 3 study

was carried out by the US ECOG intergroup (E4494) study comparing six to eight cycles of CHOP versus R-CHOP in elderly patients with aggressive lymphoma, which included a second randomization in CR patients comparing observation and rituximab maintenance therapy every 6 months for 2 years. Unlike the GELA study, there was no response rate or OS difference detected, although there was a benefit in TTF for the R-CHOP arm. The analysis was confounded to some extent by the secondary randomization to maintenance versus no-maintenance rituximab. Maintenance therapy was beneficial for the TTF only in the CHOP-induction subset. As such, interpretation of these results supports the use of R-CHOP induction without subsequent maintenance rituximab therapy.

Two other randomized controlled studies have been published supporting the benefit of the addition of rituximab to anthracycline-based chemotherapy in DLBCL. The MabThera International Study Group (MInT) study included young (<60 years), low-risk (aaIPI 0 or 1) patients with DLBCL (including PMBCL) who primarily received either CHOP or CHOP plus etoposide (CHOEP) with or without rituximab. The rituximab-containing regimens demonstrated an improvement in EFS and OS (Pfreundschuh et al., 2006) (Table 21-12). The Rituximab With CHOP Over Age 60 Years (RICOVER-60) trial by the same group evaluated CHOP-14 for six or eight cycles, with or without rituximab in elderly patients and also demonstrated a significant improvement in all endpoints with the rituximab combinations (Pfreundschuh et al., 2008). Of note, the latter study also established that six cycles of R-CHOP-14 was associated with the best outcome. Although, six versus eight cycles of R-CHOP-21 have not been compared, six should be preferred in most circumstances to minimize toxicities.

Two randomized studies (GELA LNH-03-6B and the British National Cancer Research Institute [NCRI]) compared R-CHOP-21 (ie, repeated every 21 days) with R-CHOP-14 (every 14 days), and there was no improvement of FFS or OS using the of the shortened cycle interval, thus confirming that R-CHOP-21 remains the standard (Table 21-12). Based upon the observation that elderly females fare better with R-CHOP than do elderly males, and that elderly males clear rituximab more rapidly, dose-dense rituximab regimens are being tested in elderly males. A trial where elderly males were treated with higher dose of rituximab given at 500 mg/m^2 while females received standard dose of 375 mg, showed that outcomes of male patients treated with high dose rituximab was equivalent to outcomes of females. However, this was not a randomized study of different rituximab doses, and a confirmatory phase 3 trial would need to be conducted before the standard practice is changed. This observation,

Table 21-12 Key trials of diffuse large B-cell lymphoma using rituximab-containing regimens

Author (trial/phase)	*N*	Treatment	Patient selection	PFS/EFS	OS
Coiffier et al. (GELA/III)	202	R-CHOP × 8 vs ×	Age 60-80 y	57% vs 38% (2 y)	70% vs 57% (2 y)
	197	CHOP × 8	Stage II-IV	35% vs 20% (10 y)	43.5% vs 28% (10 y)
Pfreundschuh et al.	413	R-CHOP-like* × 6 vs	Age 18-60 y	79% vs 58% (3 y)	93% vs 84% (3 y)
(MInT/III)	410	CHOP like* × 6	aaIPI 0 or 1	74% vs 56% (6 y)	90% vs 80% (6 y)
			Stage I(+bulk or II-IV)		
Pfreundschuh et al.	306	R-CHOP-14 × 6	Age 61-80 y	66.5% (3 y)	78% (3 y)
(RiCOVER-60/III)†	304	R-CHOP-14 × 8	Stage I-IV	63% (3 y)	72.5%(3 y)
	209	CHOP-14 × 6		47% (3 y)	68% (3 y)
	219	CHOP-14 × 8		53% (3 y)	66% (3 y)
Cunningham et al. (ASCO 2011)	540	R-CHOP-21 × 8	Age 61-80 y	81% vs 83% (2 y)	81% vs 83% (2 y)
(NCRI/III)	540	R-CHOP-14 × 6 + G-CSF			
Delarue et al. (ASCO 2012)	296	R-CHOP-21 × 8	Age 60-80 y	60% vs 56% (3 y)	72% vs 69% (3 y)
(LNH03-6B/III)	304	R-CHOP-14 × 6	aaIPI >1		
Recher et al. (LNH03-2B/III)	196	R-ACVBP	Age 18-59 y	87% vs 73% (3 y)	92% vs 89% (3 y)
	183	R-CHOP	aaIPI 1		
Wilson et al. (NCI/II)	72	DA-EPOCH-R	Age >18 y	79% (5 y)	80% (5 y)
			Stage II-IV		

Survival estimates shown for rituximab-containing regimens only and are rounded off where applicable to the nearest whole number.
EFS = event free survival; G-CSF = granulocyte colony-stimulating factor; GELA = Groupe *d'Etude des Lymphomes de l'Adulte;* PFS = progression-free survival; MInT = MabThera International Study Group; NCRI = British National Cancer Research Institute Study; OS = overall survival; R = rituximab; RiCOVER-60 = rituximab with CHOP Over Age 60 Years; y = year.
*87% DLBCL; CHOP-like = CHOP-21 or CHOEP-21 in 92%; radiotherapy given to sites of bulk, extranodal disease (physician's discretion).
†80% DLBCL.

however, highlights a need for comparing equivalent doses of monoclonal antibodies in randomized clinical trials.

Treatment of limited-stage DLBCL

Approximately 25% of cases of DLBCL are limited stage, which typically includes patients with stage I disease and nonbulky (<10 cm) stage II disease. Some groups or studies also will include patients with bulky stage I disease and exclude patients with B-symptoms. A large randomized SWOG trial (SWOG-8736) established that CMT was superior to CHOP alone for the treatment of localized (stage I(E), non-bulky stage II(E)) aggressive lymphoma (Miller et al., 1998). In this study, the 5-year PFS (77% vs 65%, $P = 0.03$) and OS (82% vs 72%, $P = 0.02$) for three cycles of CHOP followed by IFRT was superior to that of eight cycles of CHOP alone. An update of the study with longer follow-up, however, showed that the treatment advantage for the CMT was not sustained because of an excess of late relapses, which was offset by increased toxicity in the chemotherapy-alone arm. A stage-adjusted IPI has been proposed for limited-staged disease that includes stage II disease, age >60 years, PS >2, and elevated LDH as risk factors. The 5-year OS rates reported in the updated follow-up for patients with 0, 1 or 2, and 3 risk factors were 94%, 71%, and 50%, respectively.

The benefit of rituximab has not been specifically analyzed in a randomized controlled trial in localized DLBCL. The MInT study did include some patients with localized disease by nature of the inclusion criteria. The SWOG completed a phase 2 study evaluating three cycles of R-CHOP, with four doses of rituximab, followed by IFRT (40-46 Gy if CR and 50-55 Gy if PR) in patients with localized aggressive B-cell lymphoma, the majority of who had DLBCL. Patients had to have at least one risk factor by the stage-modified IPI (Persky et al., 2008). The study population was similar to the SWOG study described earlier, enabling a historical comparison to determine the impact of the addition of rituximab to CMT. The 2-year PFS was superior in the R-CHOP patients (95% vs 83%).

With potential acute and more concerning long-term side effects of radiotherapy, there has been interest in whether a subgroup of patients with limited-stage DLBCL can be selected to receive chemotherapy alone. Mature, conclusive data is lacking. However, a preliminary report of a randomized clinical trial does suggest that RT can be safely omitted in selected patients (Lamy et al., 2014). Patients with limited stage, nonbulky (<7 cm) DLBCL were randomized to 4-6 cycles of R-CHOP or 4-6 cycles of R-CHOP followed by 40Gy RT. Patients in CR by PET imaging after four cycles (84%) did not receive cycles five and six of R-CHOP. The patients assigned to no RT had EFS and OS that was not different compared to patients receiving RT, suggesting RT may be unnecessary in selected patients.

Novel strategies to improve cure rates in DLBCL

Although the outcome of DLBCL has improved with R-CHOP chemotherapy, ~40% of patients fail after primary therapy. The majority of patents with relapsed DLBCL succumb to the disease. There are several ongoing approaches to improve outcome in DLBCL, including the use of a new combination chemotherapy backbone (eg, ACVBP, DA-EPOCH), novel enhanced anti-CD20 monoclonal antibody (eg, obinutuzumab [GA101], ofatumumab), maintenance therapy, and adding novel targeted agents to R-CHOP (so called XR-CHOP, where X represents novel agent).

A phase 3 randomized controlled trial (LNH03-2B) comparing the dose-intensive regimen R-ACVBP (doxorubicin [Adriamycin], cyclophosphamide, vindesine, bleomycin, and prednisone) with sequential consolidation (methotrexate, rituximab/etoposide/ifosfamide, cytarabine) with standard R-CHOP in patients with DLBCL 18-59 y and only one adverse prognostic factor by the aaIPI (Recher et al., 2011). The dose-intensive regimen was associated with a more favorable PFS and OS but with higher toxicity.

In North America, dose-adjusted (DA)-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) currently is under evaluation in the management of DLBCL. A phase 3 trial in newly diagnosed DLBCL, with biomarker analysis to evaluate outcomes in the ABC and GCB subtypes has been completed and the analysis of the results is ongoing. Although generally well tolerated, DA-EPOCH-R is associated with greater toxicity than R-CHOP, with hospitalization for febrile neutropenia occurring in 19% of cycles, despite mandatory granulocyte colony-stimulating factor (G-CSF) support.

New anti-CD20 antibodies also are being studied in a variety of B-cell lymphomas, including GA-101. In contrast to rituximab, obinutuzumab (GA-101) has enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) and increased direct cell death induction but low-complement dependent cytotoxicity (CDC). A phase 3 study comparing R-CHOP to G-CHOP (GOYA) for the first-line treatment of advanced stage DLBCL has been completed and is maturing for analysis.

Several novel, targeted agents have been shown to have significant activity in relapsed and refractory DLBCL, including bortezomib, lenalidomide, and ibrutinib. These agents were combined with R-CHOP (Bor-R-CHOP, R2-CHOP and IR-CHOP respectively). Due to mechanism of action of these compounds on either BCR signaling or downstream, these combinations are particularly promising in ABC subtype of DLBCL. All 3 "XR-CHOPs" are currently being evaluated in large randomized studies. While some of the studies allow patients with all subtypes of DLBCL, other limit eligibility to patients with non-GCB DLBCL defined by

IHC or novel, real time GEP techniques, like Lymph2CX using Nanostring platform.

Primary transplant in advanced-stage DLBCL

It has been proposed that patients in IPI poor-risk groups might benefit from a more aggressive treatment approach, such as HDC and ASCT or alloSCT. A recent European phase 3 randomized trial in aggressive NHL patients tested eight cycles of CHOP versus two cycles of cyclophosphamide, epirubicin, vindesine, and prednisone followed by HDC and ASCT and found higher 5-year EFS for patients in the transplantation arm. There was an OS benefit for transplantation in a subgroup analysis confined to the high-intermediate IPI risk patients. The role of ASCT in frontline therapy for DLBCL, however, remains unclear in the era of rituximab. The SWOG group conducted a randomized phase 3 study investigating the benefit of HDC/ASCT in first remission in patients with advanced-stage diffuse large-cell NHL with an aaIPI 2 or 3. This study was initiated in 1997 and did allow patients with a T-cell phenotype although by disease frequency, the majority of patients had DLBCL. The initial induction regimen was five cycles of CHOP ($n = 215$); however, this was amended to R-CHOP ($n = 182$) in DLBCL patients in 2003 to align with the new standard of care. Patients in at least a PR after five cycles of R-CHOP were randomized to receive either three further cycles or autotransplant using total body irradiation (TBI) or BCNU (carmustine)-based regimens. In the intention to treat (ITT) analysis, the 2-year PFS favored transplant (69% vs 56%, $P = 0.005$), however, there was no difference in the 2-year OS (74% vs 71%, $P = 0.32$). Of note, 18% of patients in the standard arm subsequently underwent treatment with salvage therapy and ASCT at relapse. In exploratory analyses, there was no differential treatment interaction by phenotype (B- vs T-cell) or induction regimen (CHOP vs R-CHOP). Patients with high-risk aaIPI, however, had a superior PFS and OS (2-year 82% vs 64%) in the transplant group. Given the lack of OS for the group as a whole, primary transplant is still considered experimental in the primary therapy setting even in high-risk subgroups.

Management of relapsed and refractory DLBCL

Given the implications of recurrent DLBCL, efforts should be undertaken to obtain a diagnostic biopsy unless there is unequivocal progression on imaging. In addition, some patients may relapse with indolent lymphoma, which would be managed very differently. Following confirmation of recurrence, patients should undergo full restaging investigations. If the patient does not have significant comorbidities and is <70 years of age (<75 in some centers), second-line (salvage) combination chemotherapy regimen should be given such as ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, AraC, cisplatin), or GDP (gemcitabine, dexamethaxone, cisplatin) followed by HDC/ASCT if chemotherapy-sensitive disease is demonstrated. The evidence supporting the use of HDC/ASCT in relapsed DLBCL is based on the PARMA study. Patients who relapsed with aggressive lymphoma (excluding CNS or bone marrow involvement) following an initial CR to primary therapy, received two cycles of DHAP salvage chemotherapy. If chemosensitivity (ie, a PR or CR to salvage chemotherapy) was demonstrated, patients were then randomized to receive either further chemotherapy with DHAP or HDC with BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) and ASCT. The transplant arm resulted in an improvement in both the 5-year EFS (46% vs 12%, $P = 0.001$) and OS (53% vs 32%, $P = 0.038$).

The optimal salvage therapy recently has been investigated in two phase 3 randomized controlled trials. The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study randomized patients with relapsed DLBCL (or those who had not achieved a CR) to receive R-DHAP or R-ICE for three cycles followed by HDC (with BEAM)/ASCT if a response was demonstrated. There was also a second randomization following transplant to either rituximab or observation to evaluate the role of maintenance therapy (Gisselbrecht et al., 2010). At diagnosis, 62% of the patients had been treated with a CHOP-like regimen with rituximab. The ORR was similar between R-DHAP and R-ICE (63% vs 63.5%), and there was no difference in either EFS or OS and maintenance rituximab did not affect outcome. Patients who previously had received rituximab with their primary therapy had an inferior response rate (51% vs 83%, $P < 0.001$) and 3-year EFS (21% vs 47%), suggesting that this represents a very chemoresistant group. Additional poor prognostic factors that emerged from this study were early relapse <1 year and an aaIPI of 2 or 3. Interestingly, a subsequent correlative study suggested that patients with GCB DLBCL had an improved outcome to R-DHAP compared with R-ICE (3-year PFS 52% vs 32%, $P = 0.018$), which was even more striking if cases were defined by gene expression profiling (GEP) (3-year PFS 100 % vs 27%), but the numbers were small. These results suggest selective drug sensitivity in molecular DLBCL subtypes but await confirmation in other data sets. A second phase 3 trial was conducted by the NCIC (National Cancer Institute of Canada) comparing DHAP to the outpatient salvage regimen GDP (gemcitabine, dexamethasone, cisplatin) in aggressive lymphomas using a noninferiority design. In 2005, the protocol was amended for aggressive B-cell lymphomas to include rituximab with each salvage regimen. The ORR, EFS, and OS was similar between the treatment arms, but (R)-GDP

was associated with less grade 3 or 4 toxicity ($P = 0.0003$), including, febrile neutropenia (9% vs 23%, $P < 0.0001$) and patients had superior QOL scores.

There is very little information regarding the effectiveness of salvage therapy in patients with refractory disease, which typically is defined as either progressive disease (PD) on primary therapy or relapse within 3 months. In the CORAL study, only 11% of patients had PD on primary therapy. Limited studies suggest that these cases are rarely responsive to salvage therapy and most often are unable to undergone HDC/ASCT. Further patients with chemo-resistance to second-line therapy also have a very poor prognosis, and these high-risk groups should be considered for investigational therapies.

Management of nontransplant-eligible patients with relapsed or refractory DLBCL, including novel therapies

Many patients are not eligible for curative intent treatment with salvage chemotherapy and HDC/ASCT due to advanced age or comorbidities. Given that the goal of treatment in this setting is typically palliative, single-agent chemotherapy often is used because it is less toxic than combination regimens. Use of the salvage regimens outlined previously in this typically older group of patients usually is quite toxic, and it is unknown whether these regimens prolong OS. The exception is select cases with late relapses or low-secondary IPI risk score, which rarely may be cured with a salvage combination regimen. Gemcitabine and etoposide have been used in the palliative setting in addition to oral low-dose chemotherapy (metronomic) with good tolerance and modest response rates. Rituximab often is added to chemotherapy, although there is no firm data showing improved outcome. Palliative radiotherapy can be effective for localized, symptomatic disease. A number of novel, targeted agents show significant clinical activity in DLBCL. Interestingly, due to targeted nature of these, often the activity appears to be molecular subtype specific. For example, lenalidomide and ibrutinib showed significant activity in relapsed and refractory DLBCL and appears to be particularly active in ABC (non-GCB) DLBCL. There are many more agents under investigations for this patient population and entry into a clinical trial should be strongly encouraged if the patient's PS is still good.

Special situations: management of specific clinicopathologic entities of DLBCL

Primary mediastinal (thymic) large B-cell lymphoma

PMBCL was recognized as specific entity in the WHO classification based on unique clinicopathologic presentation. Patients are typically females with a median age of 35 years who present with a bulky anterior mediastinal disease that can be locally invasive into the lung and chest wall occasionally with symptoms of superior vena cava syndrome. Distant spread is uncommon at diagnosis. At relapse, involvement of unusual extranodal sites can occur in PMBCL, including the kidneys, adrenals, ovaries, liver, spleen, and CNS.

Histologically, sclerosis is typically present, and phenotypically, the cells may lack surface immunoglobulin expression but express B-cell markers, such as CD19 and CD20. CD30 is present in 80% of cases; however, it is usually weak and heterogeneous. Interestingly, recent gene expression analysis has shown that PMBCL is molecularly distinct from typical DLBCL and shares many components of the molecular signature with cHL. It had long been speculated that there may be a pathogenic overlap between the nodular sclerosis subtype of cHL based on shared clinical features, including a young age of onset and mediastinal predominance, as well as pathologic features, including predominant fibrosis and tumor cells that are $CD30^+$. In addition, composite and sequential lymphomas have been reported, and a GZL with overlapping features of both malignancies is now defined in the WHO (see the section "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL"), further highlighting the biological continuum between these diseases.

A novel recurrent translocation involving *CIITA* (MHC class II transactivator) was found to be recurrent in PMBCL, occurring in 38% of patients and also found in 15% of cHL (Steidl et al., 2011) (Table 21-2). Cases with these chromosomal breaks had an inferior disease-specific survival. Prior studies also found reduced expression of MHC class II genes, and this also is linked to an inferior outcome.

The outcome of patients with PMBCL is favorable and was so even in the prerituximab treatment era (5-year OS, 70%; Savage et al., 2006), although patients have primary refractory disease and very low cure rates. Rituximab appears to improve outcomes further. The MiNT study included 87 patients with PMBCL, which confirmed an improved CR(u) rate, a reduction of PD, and an improvement in 3-year EFS (78% vs 52%, $P = 0.001$) with the addition of rituximab to CHOP-like chemotherapy, but the OS was similar (89% vs 78%, $P = 0.158$) (Rieger et al., 2011). Consolidative involved field radiation is typically administered after R-CHOP therapy. DA-EPOCH-R (without radiation) also has been evaluated in a phase 2 study showing encouraging results with a median follow-up of 5 years (EFS 93% and OS 97%) (Dunleavy et al., 2013). DA-EPOCH-R without radiation and R-CHOP plus IFRT are considered reasonable standards in PMBCL. Given that many patients are young females, the avoidance of radiation is an attractive notion in PMBCL.

Studies are ongoing investigating whether PET scanning can be used to select patients who may benefit from

consolidative radiotherapy and conversely spared if they are in a CR. The role of RT in this setting is unclear and the International Extranodal Lymphoma Study Group (IELSG) has initiated a randomized trial (IELSG37), whereby patients who are PET negative after a rituximab-containing regimen are randomized to observation versus radiotherapy.

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL

In the updated WHO 2008, a new category was defined that shows overlapping clinical, morphological, or immunophenotypic features between cHL and DLBCL, particularly PMBCL. These cases of so-called GZL usually occur in young men between 20 and 40 years old who present with an anterior mediastinal mass and may have supraclavicular lymph node involvement. A broad spectrum of cytological appearance can occur within the same tumor. The immunophenotype often is transitional between PMBCL and cHL (see Chapter 20) with the tumor cells $CD45^+$, $CD20^+$, $CD30^+$, and $CD15^+$. Cases of morphologically nodular sclerosis cHL with strong and uniform expression of CD20 and CD15- would favor a diagnosis of GZL. In contrast, cases resembling PMBCL but that are CD20– and CD15+ or EBV+, also would support GZL. Given disease rarity, there is little information regarding clinical outcome or optimal therapy. Small series suggest these are best managed like other aggressive NHLs rather than like HL.

T-cell-rich DLBCL

T-cell rich DLBCL is an uncommon variant of DLBCL. Typically, the neoplastic cells comprise <10% of cellular population and are outnumbered by a background of abundant T-cells and histiocytes. Histologically, it can resemble nodular lymphocyte predominant HL. Typical presentation includes middle-aged men often with an advanced disease at diagnosis and liver and spleen involvement. The treatment with R-CHOP results in similar results to these seen in other subtypes of DLBCL.

"Double-hit" DLBCL (DHL)

Five to 10% of DLBCL patients have "double-hit" lymphoma (DHL), defined as presence of c-*myc* and either *bcl2* or *bcl6* translocations (detected by FISH). These high-risk patients have lower OS when treated with R-CHOP. As such, R-CHOP is considered an inadequate therapy for DHL, with majority of patients dying within 2 years of the diagnosis (Petrich et al., Blood 2014).

The majority of patients present with poor prognostic features, including an advanced age, elevated LDH, and an advanced stage often with extranodal involvement, including CNS. Due to inadequacy of R-CHOP, various intensified chemoimmunotherapy strategies have been proposed, largely based on experience in Burkitt lymphoma; however, advanced age of patients and often poor performance status limits the use of intensive chemotherapy. Due to its rarity, data largely come from retrospective reviews, and as such comparison between regimens is difficult. The intensified including HyperCVAD and CODOXM/IVAC appear to compare favorably with R-CHOP historical controls; however, one must bear in mind that patients who are candidates for such intensive therapy are frequently younger and have better PS, as such results may not be generalizable to majority of patients with DHL. A study presented at ASH 2014 by Dunleavy et al utilizing R-EPOCH in a multicenter phase 2 study which included DHL demonstrated a promising early PFS (87% at 14 months). R-EPOCH is usually better tolerated than other intensified regimens, therefore might be offer an option for patients who are not a candidates for intensive chemoimmunotherapy or ASCT. Novel agents, particularly those targeting BCL2, may offer a promise in DHL and are under investigation.

Key points

- Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of NHL.
- The IPI and cell of origin phenotype remain prognostic in the rituximab treatment era in DLBCL. Studies are ongoing whether patients classified as high risk by the IPI or ABC phenotype should be treated with an alternate therapy other than R-CHOP.
- Treatment with R-CHOP-21 (ie, repeated every 21 days) for six cycles is a standard of care in advanced disease; the role of consolidative radiation in advanced disease is not well defined.
- In limited stage disease, abbreviated chemotherapy with 3-4 cycles of R-CHOP plus involved-field radiotherapy (IFRT) can be used.
- Presence of relapsed disease should be documented by biopsy whenever possible.
- Transplant eligible patients with relapsed DLBCL are usually treated with salvage chemotherapy (RDHAP, RICE, and RGDP appear to have similar efficacy) followed by high dose chemotherapy and stem cell transplantation.
- PMLBCL patients are treated with DAEPOCH-R without RT or R-CHOP plus IFRT. There are no randomized studies directly comparing these approaches.
- Double-hit lymphoma (DHL) represents particularly poor prognostic category when treated with R-CHOP; the role of more intensive regimes remains to be established.

Primary CNS lymphoma

PCNSL can occur in the brain parenchyma, spinal cord, eye (ocular) (Figure 21-3), cranial nerves, or meninges. Of note, although 95% of cases of PCNSL are DLBCLs, rare cases of

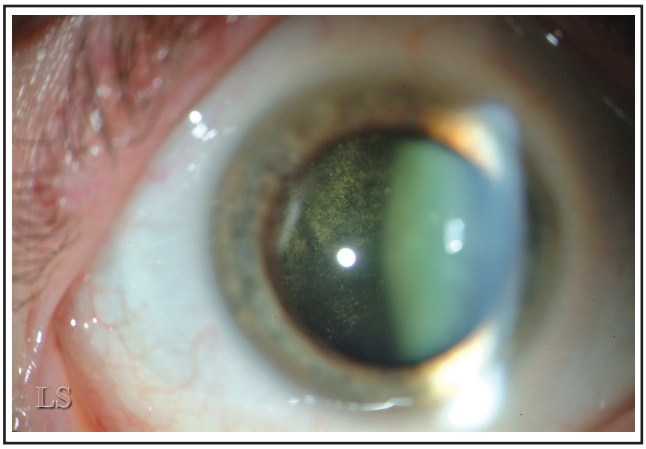

Figure 21-3 Intraocular large B-cell lymphoma on slit lamp examination.

PTCL, low-grade lymphoma, and BL also have been reported. In addition to B-cell markers, CD10 expression is observed in only 10%-20%, but BCL6 expression is common (60%-80%). PCNSLs are rare and may occur in immunocompetent patients or in association with immunosuppression related to HIV infection or organ and marrow transplantation. With the introduction of highly active retroviral therapy (HAART), the incidence of PCNSL has decreased in HIV-infected persons. It appears, however, to be increasing in incidence in immunocompetent patients. In the latter group, the median age is 60 years, and it is discovered based on focal neurologic symptoms, personality changes, or symptoms of increased intracranial pressure. Ocular involvement can occur in 10%-20% of patients and may be the sole site of disease at presentation (intraocular lymphoma). Concurrent leptomeningeal disease is found in 16% through CSF analysis but occurs as the sole site in <5%. B symptoms are extremely uncommon and should raise suspicions of systemic involvement (reviewed by Ferreri, 2012).

Stereotactic-guided biopsy is the optimal method to diagnosis CNS lymphoma, and gross total resection should be avoided. Steroids can interfere with pathologic diagnosis, and if they are started for neurologic symptoms, they should be withheld in patients with a presumptive radiologic diagnosis of CNS lymphoma to increase diagnostic biopsy yield. A contrast-enhanced MRI should be performed, along with lumbar puncture with CSF analysis. A slit-lamp examination should be performed to rule out concurrent ocular involvement. Staging should include CT imaging, bone marrow aspirate and biopsy, and, in men, testicular ultrasound, as 4%-12% of patients can have extraneural disease.

A prognostic scoring system has been developed in PCNSL given the limitations of the Ann Arbor staging system and the IPI in this disease. The following five factors are associated with a poor prognosis: age >60; PS >2; elevated LDH; high CSF fluid protein concentration; and tumor location within the deep regions of the brain. Patients with 0, 1 to 4, or 5 of these factors have a 2-year OS rate of 80%, 48%, or 15%, respectively.

The median survival after surgery alone is ~1-4 months. Whole-brain radiation is associated with a high response rate of 90%, but the median survival is only 12 months. CHOP has poor CNS penetration and should not be used in PCNSL. The exception is intravascular large B-cell lymphoma with CNS involvement as the mechanism of spread is likely different. Although there have been no randomized controlled studies to establish the best therapy, in retrospective analyses, outcomes are superior when high-dose methotrexate (HD-MTX) (3-8 g/m^2) is incorporated into first-line regimens. With this approach, the 5-year OS is approximately 30%-40%. Some studies have added other CNS-penetrant chemotherapy drugs, such as cytarabine (ara-C). Rituximab has poor penetration across the blood–brain barrier but is currently being tested in clinical trials given synergy with chemotherapy. A phase 3 trial randomizing younger patients in a CR following HD-MTX to either WBRT (45 Gy) versus observation demonstrated an improvement in median PFS (18 months vs 12 months) but OS was similar (reviewed in Ferreri, 2012). For older patients >60 years, the risk of neurotoxicity is considerable and manifests as dementia, ataxia, and incontinence, with a median time to onset of approximately 1 year. With concerns of neurotoxicity, even in younger patients, numerous studies are evaluating chemotherapy alone with CNS-penetrant drugs. The CALGB evaluated the combination of HD-MTX, temozolomide, and rituximab with consolidative HDC using ara-C and etoposide without WBRT and the 3-year PFS and OS were 50% and 67%, respectively. Studies are also investigating lower doses of radiation in patients in a CR after chemotherapy. If chemotherapy is contraindicated because of age or comorbidities, WBRT (40-50 Gy) is recommended.

HDC/ASCT has been evaluated in the upfront and salvage setting. Several small phase 2 studies have evaluated upfront transplant with cure rates ranging from 40% to 77% using a variety of lead-in chemotherapy and HDC regimens. There are two ongoing randomized trials comparing WBRT and HDC/ASCT. In patients with relapsed or refractory primary CNS, HDC/ASCT is associated with a 2-year OS of 45%, a TRM of 16%, and severe neurotoxicity in 12%. Currently, it should be considered experimental but may be appropriate in select young patients in the relapsed setting. Temozolomide either alone or in combination with rituximab has shown an ORR of 26% and 53%, respectively, in relapsed and refractory patients. The combination of high-dose methotrexate, rituximab, and temozolomide (MRT) is well tolerated and associated with significant activity in a recently reported small phase 2 study. CR was achieved in 14/18 (78%) patients at a median of 4 months. Three of 18 patients

achieved partial response (PR). At a median follow-up of 15.5 months from treatment initiation, 10/18 patients remain in CR and median PFS has not been reached.

No evidence suggests that intrathecal chemotherapy improves outcome if HD-MTX is being used; however, the CSF should be reanalyzed on treatment to ensure clearance of the malignant cells.

Secondary CNS lymphoma

The rate of secondary involvement of CNS in aggressive lymphoma varies by histology, occurring in up to 30% of BL (see section "Burkitt lymphoma" in this chapter) and lymphoblastic lymphoma. In these highly aggressive lymphomas, CNS prophylaxis is routinely incorporated using intrathecal (IT) and systemic chemotherapy with or without cranial irradiation and has been shown to reduce the rate of CNS relapse and prolong survival. Secondary CNS lymphoma also is seen in DLBCL occurring in the brain parenchyma, leptomeningeal compartment, or both, as an isolated event, or with systemic relapse. The overall risk of CNS relapse and progression in DLBCL is only ~5% but can be up to 25%-30% in specific high-risk subgroups. A number of extranodal sites have been associated with a higher risk of CNS relapse, including testis, breast, kidney, and bone marrow (concordant).

Although these and other studies can effectively identify subgroups with a high risk for CNS disease, demonstrating a benefit for CNS prophylaxis has proven to be much more difficult in DLBCL. Furthermore, many of the studies evaluating CNS prophylaxis were published before the routine use of rituximab, which does appear to reduce risk, albeit to a modest degree. The RiCOVER-60 study evaluated 1,217 patients with aggressive lymphoma (81% DLBCL) and reported that 58 patients (4.8%) developed CNS relapse or progression with a median time of 8 months (1-39 months) with a median survival from CNS relapse of only 3 months. Those patients who received rituximab had a lower risk of CNS relapse; however, the magnitude of difference was very small (3.6% vs 5.9%, $P = 0.043$). Other studies have confirmed that rituximab appears to reduce the risk of relapse, particularly in patients in a CR, suggesting the benefit in part may be due to better systemic disease control (Villa et al., 2009). The risk is not altogether eliminated, however, given the poor CNS penetration of rituximab. Modeled after BL and lymphoblastic lymphoma, intrathecal CNS prophylaxis often is administered to high-risk DLBCL patients, but the protective benefit is unknown. Prophylactic use of HD-MTX (3.0-3.5 g/m^2) with R-CHOP was evaluated retrospectively in 65 patients with high-risk DLBCL (elevated LDH, involvement of >1 extranodal sites, 4-5 Hollender criteria, high-risk location: bone marrow, testes, epidural, liver, adrenal, renal, orbit), and reported a low rate of CNS relapse (3%) (Abramson et al., 2010). Use of HD-MTX, however, is limited in elderly patients, particularly with poor renal function. Similar strategy of systemic methotrexate prophylaxis is currently under evaluation in treatment of primary testicular DLBCL, a subset of DLBCL associated with particularly high risk of CNS relapse in the study conducted by IELSG. Of note, patients with testicular lymphoma, in addition to CNS, have a high risk of relapse in contralateral testicle, and prophylactic radiation therapy to remaining testicle is usually recommended.

Despite the limitations and lack of evidence-based data to direct treatment, patients considered high risk either by the extranodal site involved or by the Hollender risk model should be evaluated for occult CSF involvement using cytology. Flow cytometry also has been shown to be a more sensitive tool for the detection of CNS involvement and should be employed where possible to rule out CNS disease at the time of diagnosis. Those with positive findings should undergo further staging with a MRI and be treated aggressively for CNS disease. Cases negative by CSF can be considered for prophylactic strategies and where possible evaluated in a prospective clinical trial. A management algorithm has been proposed in a recent comprehensive review (Siegal and Goldschmidt, 2012).

Burkitt lymphoma

BL is among the most aggressive of all human malignancies, with a rapid doubling time, acute onset, and progression of symptoms. Histologically, BL has a diffuse growth pattern of medium-size cells and a high mitotic rate, as depicted by nearly 100% of cells being Ki-67 positive due to deregulated high-level expression of cMYC arising from reciprocal translocation with immunoglobulin-heavy (t8;14) or variant light-chain gene loci (t2;8 or t8;22) (Table 21-2). There is also a high rate of cell death or apoptosis, and the dead cells are phagocytosed by histiocytes, which gives a "starry-sky" appearance at low power. The B-cells are positive for CD19, CD20, BCL6, and CD10. BCL2 is usually negative, but rare weakly positive cases may be seen. Lack of TdT is critical to rule out ALL/lymphoma. Gene expression profiling studies show that BL has a distinct molecular signature distinguishing it from DLBCL.

Originally described in its endemic form in African children presenting with jaw or facial masses, BL also occurs in sporadic form in the Western world, predominantly in children and young adults. It also is seen in HIV-infected patients. Most endemic and some sporadic cases show evidence of EBV infection and presence of the EBV genome.

Clinically, patients with BL frequently present with a bulky abdominal mass, B-symptoms, and extranodal disease,

including bone marrow involvement, is common (up to 70%). A leukemic phase can be seen, but pure acute leukemia is extremely rare. CNS dissemination, usually in the form of leptomeningeal involvement, may be present at diagnosis in up to 40% of patients; as a result, HD-MTX and intrathecal chemoprophylaxis are integrated into the therapy for all BL patients.

Therapy for BL must be instituted quickly because of the rapid clinical progression of the disease. Admission to hospital and tumor lysis precautions are essential and include vigorous hydration and allopurinol with close monitoring of laboratory studies, including electrolytes and renal function. Early dialysis is indicated at the first signs of decreasing renal function, hyperkalemia, or hyperphosphatemia. Recently, recombinant uric acid oxidase (rasburicase) has been shown to be very effective in preventing uric acid nephropathy and its secondary metabolic complications. Multiple studies have shown that CHOP chemotherapy is inadequate for the treatment of BL, and intensified therapies result in higher cure rates. Multiagent combination chemotherapy that includes high doses of alkylating agents and CNS prophylaxis have improved the outcome for adults and children with the disease. Given disease rarity, there are no randomized controlled treatment trials in adults comparing these approaches. Magrath et al. (1996) at the National Cancer Institute demonstrated a risk-adapted strategy that is useful for treatment stratification in both adults and children. Low-risk patients were those with a single extra-abdominal mass or completely resected abdominal disease and a normal LDH, and all other patients were considered high risk. Low-risk patients received three cycles of cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M) only, and high-risk patients received CODOX-M alternating with ifosfamide, etoposide, and cytarabine (IVAC) for a total of four cycles (ie, two cycles each of CODOX-M and IVAC). All patients received intrathecal chemoprophylaxis with each cycle, and those with CNS disease at presentation received additional intrathecal therapy during the first two cycles. Approximately half of the patients were adults, and the 2-year EFS for all patients was 92%. Two other phase 2 studies have used the Magrath regimen with modifications. In a United Kingdom study, adult (age range, 16-60 years; median, 26.5 years), non-HIV patients were treated with dose-modified CODOX-M (3 g/m^2) for three cycles if determined to be low risk (ie, normal LDH, PS of 0 or 1, Ann Arbor stage I or II, and no tumor mass >10 cm), and all other patients were considered high risk and treated with alternating dose-modified CODOX-M/IVAC. The 2-year PFS for the patients with BL was 64%. At the Dana-Farber Cancer Institute, an older population (median age, 47 years) of patients was treated with a modified Magrath regimen, and the reported 2-year EFS was 71% with a modified Magrath regimen. Other therapeutic approaches have included the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HyperCVAD)/methotrexate-cytarabine regimen and ALL-type regimens. It also is unknown whether consolidative ASCT improves outcome in BL.

Given the limited data in older patients, the results from 12 large treatment series (10 prospective and 2 retrospective) were combined to better determine outcome in patients with BL in patients >40 years of age (Friedberg et al., 2005). In total, 470 patients were identified, 183 of whom were >40 years. The median OS at 2-years with intensive short-duration chemotherapy in older patients was only 39% compared with 71% when all patients were considered, suggesting an unmet need in older BL patients. The DA-EPOCH-R regimen was evaluated in 19 immunocompetent patients with BL and demonstrated an EFS rate of 95% (Dunleavy et al., 2013). This may be the preferred approach to older BL and is the subject on ongoing prospective trials. Several studies have evaluated the impact of rituximab to intensive therapy and suggest a beneficial effect.

B-cell lymphoma, unclassifiable, with features between DLBCL and BL

B-cell lymphomas with features intermediate between DLBCL and BL have morphologic and genetic features of both DLBCL and BL and typically a very aggressive course. Morphologically, it appears intermediate between DLBCL and BL with cells usually smaller than typical DLBCL but larger than typical BL with a high proliferation rate, starry-sky appearance, and an immunophentype consistent with BL. Other cases may be morphologically similar to BL but have an atypical immunophenotype or genetics. So-called double-hit lymphomas with dual translocation of c*MYC* and *BCL2* are included in this category unless they are morphologically identical to DLBCL. Unlike BL, the *MYC* partner chromosome is often non-Ig. Overall, the prognosis is poor, and for the double-hit lymphomas, the risk of secondary CNS involvement is high and they rarely are cured with standard therapy. Dose-intensive therapies, including CNS-penetrant drugs, are under investigation; please see discussion in the section "'Double-hit' DLBCL (DHL)" above.

Immunodeficiency-associated lymphoproliferative disorders

Congenital or acquired immunodeficiency states are associated with an increased incidence of lymphoproliferative disorders. The WHO classification identifies four such categories: (i) primary immunodeficiency disorders, including Wiskott-Aldrich syndrome, ataxia-telangiectasia, common

variable or severe combined immunodeficiency, X-linked lymphoproliferative disorder, Nijmegen breakage syndrome, hyper-IgM syndrome, and autoimmune lymphoproliferative syndrome; (ii) HIV infection; (iii) post–solid organ or marrow transplantation with iatrogenic immunosuppression; and (iv) methotrexate- or other iatrogenic-related immunosuppression for autoimmune disease. The lymphomas seen in these settings are heterogeneous and may include HL or, more commonly, aggressive NHL. Chédiak-Higashi syndrome also has been associated with an increased incidence of pseudolymphoma and true NHL.

Lymphoproliferative disorders associated with primary immune deficiencies (PIDs) most commonly are seen in pediatric patients and frequently are associated with EBV infection. Extranodal disease including the CNS is common. Lymphomas occurring in patients with PID do not differ morphologically compared with immunocompetent hosts. DLBCL is the most frequent histologic type, although T-cell lymphomas are more common in ataxia-telangiectasia. EBV-related lymphomatoid granulomatosis is associated with Wiskott-Aldrich syndrome. These malignancies respond poorly to standard therapy. Therapy depends on both the underlying disorder and the specific lymphoma subtype; allogeneic transplantation has been used successfully in some patients. Novel immunotherapeutic or pharmacologic strategies targeting EBV are being explored.

HIV-associated lymphomas

HIV-associated lymphomas are typically DLBCL or BL. Approximately two-thirds of cases are EBV associated, and many carry a *cMYC* oncogene translocation. CNS involvement is frequent. Outcomes for HIV associated lymphomas were historically poor. However, the era of highly active antiretroviral therapy (HAART), outcomes are similar to non-HIV lymphoma, as long as the HIV is under good control and the CD4 count is over 200 cells/uL. Given the importance of optimal HIV control, HAART is usually given concurrently with chemotherapy and in communication with the HIV specialist to avoid antiretrovirals that can exacerbate chemotherapy toxicity.

The optimal chemotherapy and the role of rituximab with anthracycline combinations in HIV-associated DLBCL have been the subject of debate. One small randomized study conducted by the AIDS Malignancy Consortium (AMC 010) demonstrated no improvement in outcome comparing R-CHOP with CHOP and an increase in treatment-related infectious deaths. A subsequent analysis, however, indicated that the toxicity was higher in patients with a CD4 count <50. Furthermore, a phase 2 French study using R-CHOP in HIV-positive aggressive lymphomas (85% DLBCL) demonstrated a 2-year OS of 75% without an increase in life-threatening infections, which also may reflect the exclusion of poor-prognosis patients because patients could have no more than one of the following: CD4 <100, PS >2, or prior AIDS. Thus, rituximab should be given to HIV patients if the CD4 count is >50, particularly given the strong evidence in the HIV-negative setting. Concurrent administration of G-CSF is advised given the high rate of infection in this population. DA-EPOCH has been tested in HIV-aggressive lymphoma, the majority of which had DLBCL but with suspension of HAART to avoid any drug interactions. At 53 months, the PFS and OS were 60% and 73%, respectively. The AMC also tested EPOCH-R (AMC 034) in patients with HIV-positive aggressive B-cell lymphomas with rituximab given either concurrently or sequentially, and the 2-year OS rate was 63% and 66%, respectively. HAART use was at the discretion of the treating physician but was used in the majority of patients. There was no greater risk of infection except in patients with a CD4 <50 (Sparano et al., 2010). More recently, the NCI piloted a second-generation regimen short course SC-EPOCH-RR (dose-dense rituximab), with G-CSF support, in HIV-positive DLBCL patients in the hope of improving efficacy but reducing toxicity. Dose-dense rituximab was intended to enhance the chemotherapy and minimize the number of treatment cycles. HAART was suspended during treatment. A PET scan was performed after two cycles: if negative, only one further cycle was given; and if positive, two to three cycles were given. The 5-year PFS and OS were 84% and 64%, respectively. A pooled analysis of these two AMC trials with patients either treated with R-CHOP or R-EPOCH suggested that patients receiving R-EPOCH had an improved EFS and OS after adjusting for the aaIPI and CD4 count. The TRM was greater in patients with CD4 counts <50 (37% vs 6%, $P = 0.01$) regardless of the regimen used. It remains unclear whether HAART is mandatory during chemotherapy; however, with the possible exception of the SC-EPOCH-RR, studies support continuing HAART in patients treated with a variety of regimens, including Hyper-CVAD, CDE (infusional cyclophosphamide, doxorubicin, etoposide), EPOCH-R, and R-CHOP, particularly because newer antiretrovirals have fewer drug interactions than in the past. Use of zidovudine is avoided because of increased risk of myelosuppression and the potential for deleterious drug interactions.

Management of BL has historically been extremely challenging in the HIV population due the comorbidities combined with the required intensity of lymphoma therapy. AMC 048 reported encouraging results using a modified CODOX-M/IVAC for HIV-positive BL. The major modification was a reduction in the methotrexate dose to 3 gm/m^2. Use of HAART therapy was optional. The 2-year OS was 69% and tolerability was acceptable.

Posttransplant lymphoproliferative disorders

Posttransplant lymphoproliferative disorders (PTLDs) occur as a consequence of immunosuppression in recipients of solid organ, bone marrow, or stem cell allograft. The risk is higher in solid organ transplants that warrant a higher degree of immunosuppression (10%-25% in heart and lung transplant) than those that require a lower immune suppression dosing (1%-5% kidney and transplant). PTLDs are composed of a spectrum of disorders, ranging from EBV-positive infectious mononucleosis (early lesions) to polymorphic PTLDs, which most often are clonal to full-blown monomorphic PTLDs that can be either EBV positive (common) or EBV negative and are further subdivided into B-cell lymphomas (common) and T-cell lymphomas (rare), and are indistinguishable from their counterparts in immunocompetent hosts. HL-type PTLDs also can occur; however, indolent B-cell lymphomas arising in transplantation recipients are not among the PTLDs. EBV-negative PTLD has increased over the last decade and typically is late onset (median time from transplant to PTLD of 50-60 months vs 12 months in EBV positive), has a poorer response to therapy, and is more frequently monomorphic.

PTLDs have diverse clinical presentation depending on location. Extranodal involvement is common, particularly the gastrointestinal (GI) tract (~25%), lung, skin, and bone marrow. Primary CNS lymphoma also can occur. The goal of treatment is to cure the lymphoma but also to preserve graft function. Although a minority (20-50%) of patients will respond to a reduction in intensity of immunosuppressive drugs, most require additional systemic therapy particularly for monomorphic or late PTLDs. Tolerance to chemotherapy is poor in PTCL patients, with TRM reported to be as high as 31% in older series using CHOP chemotherapy. With historically poor tolerance to combination chemotherapy, single-agent rituximab has been explored in the first-line setting in PTLD. The ORR has ranged from 40% to 75%, and it is extremely well tolerated; however, remission duration may be short in many patients. In the first prospective phase 2 study, 43 PTLD patients who had failed to respond to a reduction in immunosuppression were treated with single-agent rituximab. The ORR was 44% at day 80 (CR 21%) and the 1-year OS was 67%. An updated analysis from this study evaluating 60 patients demonstrated an ORR of 59% (CR 42%), but the median PFS was only 6 months and the 2-year OS was 52% (Choquet et al., 2007). Elevated LDH was predictive of disease progression as well as a shorter time from the date of transplant. Using a PTLD-adapted prognostic score incorporating age (>60 years), elevated LDH, and PS (>2), patients with a score of 0, 1, or 2/3 had 2-year OS estimates of 88%, 50%, and 0%, respectively, suggesting that single-agent rituximab may be suboptimal in high-risk groups. This prompted a study in which PTLD patients failing a reduction of immunosuppression were given four weekly cycles of rituximab followed by CHOP as sequential treatment (ST). In 70 patients, the ORR was 60% following rituximab, which increased to 90% with ST with CHOP. With a median follow-up of 5 years, the median TTP and median PFS were 77 months and 48 months, respectively. The 5-year PFS was 66% and 5-year OS was 57% (Trappe et al., 2011). The TRM with CHOP was 11%. Reduced immunosuppression and single-agent rituximab are reasonable first-line treatments in the majority of patients with close surveillance and sequential therapy with R-CHOP in those who do not achieve a CR. For patients who present with very high-risk aggressive disease, R-CHOP can be considered frontline treatment with G-CSF support with strong consideration also for PCP prophylaxis.

Mantle cell lymphoma

In many ways, MCL falls between the indolent and aggressive lymphomas, unfortunately combining the poorer attributes of each; namely, the lack of curability with standard therapy and a relatively aggressive clinical course. With better recognition of MCL as a unique entity, and treatment strategies developed specifically for MCL, the median OS of MCL appears to be improving, now longer than 5 years (Hermann et al., 2009).

MCL has distinctive clinical features include median age of 64, a striking male predominance, and a strong tendency to present with advanced stage disease. Extranodal involvement is common, including bone marrow and peripheral blood, plus a peculiar tendency to invade the GI tract, which may present as a distinctive syndrome of lymphomatous polyposis of the large bowel. Even patients without overt colonic polyposis frequently have subclinical GI epithelial invasion, which can be demonstrated on biopsy.

Cytologically, the majority of MCLs consist of small lymphocytes with notched nuclei. The architectural pattern of the lymph node usually is diffuse but may show a vaguely nodular or mantle zone growth pattern. A spectrum of morphologic variants has been recognized, including small cell, which is composed of small round lymphocytes and clumped chromatin, mimicking SLL/CLL, and a blastoid variant, which has a high mitotic rate and is clinically very aggressive. The immunophenotype of MCL is distinctive. Cases are typically CD5+, FMC7+, and CD43+ but CD10− and CD23− (Table 21-2). Some of the salient features that distinguish MCL from SLL or CLL are the expression of cyclin D1 and FMC7 and the lack of CD23 expression (Table 21-2). Furthermore, MCL has a more intense IgM or IgD and CD20 expression than SLL/CLL. Virtually all MCLs carry the t(11;14)(q13;q32) on karyotypic analysis or by FISH technique. This reciprocal translocation juxtaposes the immunoglobulin heavy-chain locus and the cyclin D1 (*BCL-1*) gene.

Biologic and clinical features have prognostic value in MCL. Cellular proliferation may be the most powerful predictor. cDNA microarray analysis has demonstrated that genes associated with cellular proliferation show striking variability among MCL cases, ranging from low to very high expression. Patients in the lowest quartile of expression have median survival times of 6-8 years, whereas patients in the highest expression quartile have survivals of <1 year. For clinical practice, Ki-67 staining can provide an estimate of proliferation. Three prognostic groups have been identified using cut-points of <10% (best), 10%-29% (intermediate), and >30% (worst). With regards to clinical factors, the IPI does not provide adequate prognostic usefulness when applied to MCL, leading to the generation of an MCL-specific index (Hoster et al., 2008). The MCL international prognostic index (MIPI) identified four clinical features: age, PS, LDH, and WBC as independently associated with OS (Table 21-7). The MIPI score can separate patients into three risk groups and is quite valuable for characterizing patients on a clinical trial. It is not always useful in clinical practice, as older age and poor PS may classify a patient as "high risk," but such a patient may not be a candidate for therapy intensification.

Management of newly diagnosed MCL

There is no "standard" therapy or approach to MCL. It is a relatively uncommon lymphoma subtype (6% of new cases), making comparative trials difficult to conduct. A small number of cases have a course similar to the indolent lymphomas and a period of observation is reasonable (Martin et al., 2009). Most patients have symptomatic disease and require treatment. There are a variety of phase 2 studies in the literature, and only recently were the first randomized clinical trials reported by the European MCL Network. This group has adopted a strategy of separating patients by age and designing trials using intensive treatment strategies for younger patients (defined as age 65 or less) and nonintensive strategies for older patients (defined as age 60 or more). The 5-year overlap is intentional to allow patients between the ages of 60 and 65 to be candidates for either approach, depending on comorbidities. This strategy is a useful one for clinical practice.

For the younger patient with MCL, several different intensive strategies appear to produce comparable results. The first intensive strategy to gain widespread application was the R-HyperCVAD with alternating R-MTX/cytarabine, pioneered by investigators at the M.D. Anderson Cancer Center. This single-institution study enrolled 99 patients with a median age of 61 years. The approach produced response rates >95% and long-term follow-up revealed a 5-year PFS of ~50% (Romaguera et al., 2010). Older patients on this trial have not fared as well, with a median PFS of ~3 years and substantially more toxicity. Another intensive approach that generated highly promising results comes from the Nordic Lymphoma Study Group. They tested an intensive induction immunochemotherapy with alternating cycles of "maxi" R-CHOP and rituximab plus cytarabine followed by in vivo purge (with rituximab) and ASCT in a phase 2 trial. The study was limited to patients age <65 years and the median age was 56 years. The ORR was 96%, and the 6-year EFS and OS were 56% and 70%, respectively. Long-term follow-up demonstrated a continuing pattern of relapse, suggesting cures are not likely, even with this approach. The European MCL Network has presented results of large phase 3 randomized clinical trial in MCL patients <65 years (Hermine et al., 2010). This trial compared the efficacy of six courses of R-CHOP followed by myeloablative radiochemotherapy and ASCT versus alternating courses of R-CHOP/R-DHAP followed by a high-dose cytarabine containing myeloablative regimen and ASCT. The study was designed to test the contribution of cytarabine in the management of younger MCL patients (median age 56 years). The 3-year PFS was significantly better in the cytarabine-containing arm (75% vs 60%) and most intensive strategies now incorporate high dose cytarabine into the regimen.

Until recently, there were no trials focusing on the ~50% of MCL patients who are not candidates for an intensive therapy approach. The European MCL Network conducted a trial for patients >60 years, who were assigned randomly to induction with either R-CHOP or the R-FC (rituximab, fludarabine, cyclophosphamide) regimen (Kluin-Neilmans et al., 2012). Responding patients underwent a second randomization to maintenance therapy with rituximab (MR) or interferon-α (IFNα), each given until progression. The median age of the 560 study participants was 70 years. Although response rates were similar between R-CHOP (86%) and R-FC (79%), the OS was significantly better in the R-CHOP arm (62% vs 47% at 4 years, $P = 0.005$). The inferior survival in the R-FC group was due to a combination of inferior disease control and increased death from infectious complications related to the immunosuppressive effects of fludarabine. Remission duration was significantly longer in the rituximab group than in the IFN group. At 4 years, 58% of the MR group remained in remission compared with 29% of the IFN group. Subgroup analysis indicated the benefit of MR was restricted to the R-CHOP-treated patients, and that R-CHOP plus MR-treated patients experienced improved 4-year OS compared with R-CHOP plus IFN–treated patients (87 vs 63%, $P = 0.005$), respectively. This trial indicates that R-CHOP followed by MR is a reasonable front-line approach for older MCL patients, although emerging data suggests R-CHOP is not the best induction platform for older MCL patients.

A phase 3 trial compared R-CHOP to an R-CHOP-like regimen (VR-CAP) where bortezomib has replaced vincristine (Robak et al., 2015). The VR-CAP regimen was superior to R-CHOP for complete response rates (53% vs 42%), median PFS (24.7 months vs 14.4 months), and 4-year OS rate (64% vs 54%). The rates of neutropenia and thrombocytopenia were higher in the VR-CAP patients. The bendamustine-rituximab (BR) regimen also appears to be a preferred alternative to R-CHOP. A large randomized trial compared BR with R-CHOP in patients with newly diagnosed indolent and MCL lymphoma (Rummel et al., 2013). For the entire study population, the BR was better tolerated than the R-CHOP, with less alopecia, neutropenia, and infections. In the MCL patients ($n = 93$), median age 70, BR was superior to R-CHOP for median PFS (35 vs 22 months, $P = 0.006$). A similarly designed trial was conducted in North America (Flinn et al., 2014). MCL patients ($n = 67$) comprised a subset of the study population. MCL patients assigned to BR were more likely to achieve a complete remission than patient assigned to R-CHOP or R-CVP (50% vs 27%). Taken together, these studies suggest that VR-CAP and the BR regimen are better induction platforms than R-CHOP. Trials testing maintenance rituximab after BR are ongoing.

Management of relapsed MCL

Younger patients relapsing after intensive therapies are candidates for alloSCT. The literature varies widely in the efficacy of this approach, but it does appear to have curative potential for a fraction of patients (25%-50%). A multicenter experience using a reduced-intensity conditioning (RIC) approach demonstrated 2-year EFS and OS rates of 50% and 53%, respectively. The 2-year transplant-related mortality rate was 32%, highlighting the high-risk/high-reward nature of allogeneic SCT in relapsed MCL. For older patients, the BR regimen is highly active in relapsed MCL, with ORR of 75%-92% reported in two small studies. The proteasome inhibitor bortezomib is FDA approved for relapsed MCL and has moderate activity, with an ORR of 33% and a median PFS of 6 months. The mTOR inhibitor temsirolimus is European Union approved for relapsed MCL, demonstrating on ORR of 22% and median PFS of 4.8 months in a pivotal study. The immunomodulatory agent lenalidomide is FDA approved for recurrent MCL. In the EMERGE study ($n = 134$), lenalidomide produced response rates of 28%. Although the median PFS was just 4 months, the median duration of response of 16.6 months, indicating responder can experience durable benefit (Goy et al., 2013). Lenalidomide, which potentiates immune effector cells, appears to be even more active when combined with rituximab. A phase 1/2 trial in relapsed MCL ($n = 52$) reported an ORR of 57% and median PFS of 11.1 months (Wang et al., 2012). Most promising of the new agents is ibrutinib, a bruton's tyrosine kinase inhibitor which interferes with signaling through the B-cell receptor pathway. In a single arm phase 2 trial ($n = 111$) in relapsed/refractory MCL, the ORR was 68% with a median PFS of 13.9 months (Wang et al., 2013). Ibrutinib was FDA approved for patients with recurrent MCL in late 2013.

Peripheral T-cell lymphomas

PTCLs represent 10%-15% of all NHLs in Western populations and are a heterogenous group of mature T-cell neoplasms arising from postthymic T-cells at various stages of differentiation. NK-cell lymphomas are included in this group because of the close relationship between these two cell types. The importance of the T-cell phenotype and the impact on prognosis is now well established but is a relatively recent advance. A recent large retrospective study, the International Peripheral T-Cell Lymphoma Project (ITLP), collected 1,153 cases of PTCLs from 22 centers from around the world and highlighted the geographic, clinicopathologic, and prognostic differences of this diverse group of diseases (Vose et al., 2008).

Given disease rarity, there are no randomized controlled trials establishing that an alternate regimen is superior to CHOP, and thus CHOP remains the standard therapy of PTCLs. There is a range of disease in this category (Table 21-3), and a minority have a more favorable prognosis or a more indolent course.

Indolent PTCLs

Mycosis fungoides and Sézary syndrome

In contrast to nodal NHLs, which are mostly B-cell derived, ~75% of primary cutaneous lymphomas have a T-cell phenotype and two-thirds are either mycosis fungoides (MF) or Sézary syndrome (SS). MF is an epidermotropic, primary cutaneous T-cell lymphoma and represents the most common of all primary cutaneous lymphomas (50%). MF usually has an indolent course, but similar to indolent B-cell lymphomas, it is incurable. MF is limited to the skin in its early phases and appears as plaques or patches; but with time, it evolves to diffuse erythroderma or cutaneous nodules or tumors, usually with associated adenopathy. The early stage lesions are characteristically in a bathing suit distribution and are often pruritic in nature. Extracutaneous disease can occur in advanced stages and may indicate histologic transformation. The histology varies with stage of the disease, but epidermotropism is seen with typical plaques and intradermal collections of so-called Pautrier microabscesses. The T-cells are $CD4^+/CD8^-$, often with aberrant loss

of the T-cell antigens CD2, CD3, CD5, and CD7. Progression to nodal disease, organ infiltration, and circulating clonal T-cells (SS) represents the advanced stage of disease. A unique clinical staging system has been proposed by the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) for MF and SS. The extent of cutaneous and extracutaneous disease is the most important prognostic factor in MF, with a 10-year disease-specific survival ranging from 97% to 98% for patients with limited patch/plaque disease (<10% of skin surface; stage I) to 20% for patients for patients with lymph node involvement.

SS is a distinct disorder characterized by erythroderma, generalized lymphadenopathy, and the presence of Sézary cells in the skin, lymph nodes, and peripheral blood. It is associated with an aggressive course with a 5-year OS rate of 20%-30% with lower rates seen with high Sézary cell counts.

Because MF is incurable and the use of early therapy does not affect survival, a nonaggressive approach is recommended (reviewed Prince et al., 2009). Patients with stage IA disease may be managed expectantly with careful surveillance. If treatment is needed, topical steroids or topical nitrogen mustard, electron-beam radiotherapy, or cutaneous photochemotherapy with oral psoralen plus ultraviolet A (PUVA) typically are employed. Phototherapy with PUVA or ultraviolet B (UVB) is recommended for more widespread disease. Low-dose radiotherapy can be helpful to improve symptoms and cosmesis. Patients with progressive disease and those with systemic dissemination may be appropriately treated with methotrexate or corticosteroids, although responses are usually brief.

Combination chemotherapy regimens are not particularly effective and provide only transient responses. Single-agent treatments are preferred, particularly with slowly progressive disease, because of a high risk of myelosuppression and infection and only modest response durations seen with combination chemotherapy. Gemcitabine (ORR 48%-75%), pentostatin (ORR 28%-71%), and liposomal doxorubicin (ORR 56%-88%) have single-agent activity. Alternatively, IFNα, bexarotene, vorinostat, and denileukin diftitox all have efficacy in advanced-stage MF and SS. Bexarotene is an oral retinoid and is FDA approved for cutaneous T-cell lymphoma (CTCL). In a multicenter trial of 94 patients with advanced stage MF/SS, the ORR was 45% but with only 2% CRs. The common toxicities are hypertriglyceridemia (82%) and central hypothyroidism (29%). Denileukin diftitox is a recombinant fusion protein that combines interleukin 2 (IL-2) with the cytotoxic A chain of diphtheria toxin with an ORR of 49%. It is approved by the FDA for patients with relapsed CTCL whose tumors express the IL-2 receptor subunit (CD25). Histone deacetylase inhibitors prevent histone acetylation, thus altering the gene expression of cell-cycle and apoptotic regulatory proteins. Vorinostat and romidepsin both are approved for the treatment of CTCLs. Vorinostat is orally available and has an ORR of ~30% and a median duration of response (DoR) of ~6 months. A phase 2 trial with romidepsin demonstrated an ORR 35% (CR 6%) with a median DoR of 15 months in one study and 11 months in another. Side effects that are common with histone deacetylase (HDAC) inhibitors are fatigue, nausea, vomiting, neutropenia, and thrombocytopenia. Prolonged QT also can occur, and thus electrolytes should be monitored closely and an electrocardiogram should be performed in high-risk patients during therapy. Alemtuzumab, the humanized monoclonal antibody targeting CD52, also has been used in MF and SS with some success; however, patients are at high risk of opportunistic infections. More recent studies report single agent activity for lenalidomide (ORR 28%) and low dose pralatrexate given at 15 mg/m^2 for 3 out of every 4 weeks (ORR 45%).

Allogeneic transplant has been explored in select cases of MF and SS. The European Group for Blood and Marrow Transplantation recently reported a multi-institutional restrospective study evaluating alloSCT (myeloablative and RIC) in 60 patients with MF ($n = 36$) or SS ($n = 24$). Almost half had refractory disease at the time of alloSCT and the median number of prior regimens was four. With a median follow-up of 3 years, the 3-year PFS and OS were 34% and 53%, respectively, with higher survival rates observed in the RIC group (3-year PFS 52% vs 29%, $P = 0.006$).

Large-cell transformation in MF is defined as large cells in >25% of the infiltrate or if these cells form microscopic nodules. The incidence ranges from 8% to 39% and typically is associated with a poor prognosis, but long-term survivors can be seen. One study evaluated 100 cases of transformed MF and the median survival was 2 years with a 5-year OS and disease-specific survival (DSS) of 33% and 38%, respectively. The factors associated with a poor DSS were CD30-negative status, folliculotropic MF, generalized skin lesions, and extracutaneous transformation. Those cases with zero factors had a 2-year DSS of 83% compared with 14%-33% in patients with three or four factors. The optimal management is unclear, but for young patients, systemic chemotherapy should be used and consideration should be made for autologous or allogeneic transplantation particularly with high-risk disease. Consolidative radiation may be considered in local transformation.

Primary cutaneous ALCL

Primary cutaneous ALCL (C-ALCL) is part of a spectrum of diseases in the category of primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders that also includes

lymphomatoid papulosis and "borderline" cases that have overlapping features of both disorders. C-ALCL is the second most common type of CTCL. Patients are typically older males (median age 60 years), presenting with a solitary nodule with multifocal disease occurring in only 20% of patients. Partial or complete spontaneous regression occurs in ~25% of cases. C-ALCL must be distinguished from systemic ALCL with secondary cutaneous involvement through staging procedures.

The outcome is very favorable with a 10-year DSS of 95%. It is notable that patients with localized C-ALCL with one draining lymph node involved have a similarly good prognosis. For localized C-ALCL, radiation is the preferred therapy as the impact of chemotherapy is unknown. Progression to systemic involvement can occur in a minority of cases. For more advanced stage cases, the best management is unclear. An argument can be made to treat conservatively in minimally symptomatic patients with radiotherapy for a few lesions or low-dose methotrexate, similar to the management of lymphomatoid papulosis. If a more aggressive behavior is observed, multiagent chemotherapy is reasonable.

The anti-CD30 antibody drug conjugate (ADC) brentuximab vedotin, described further below in the section "PTCL-NOS," is being evaluated in C-ALCL, since these tumors usually express CD30. There are a variety of case reports demonstrating its efficacy.

T-cell large granular lymphocytic leukemia

T-cell large granular lymphocytic leukemia (T-LGL) is defined by a persistent (>6 months) increase in the number of peripheral blood large granular lymphocyte cells without an identifiable cause. The lymphocytosis is usually between 2 and 20 $\times$ 10^9/L. The T-cells are $CD3^+$, $CD8^+$, and CD57/CD16 and are expressed in most cases, but CD56 is negative. It arises more commonly in rheumatoid arthritis or other autoimmune disorders. Most cases have an indolent clinical course, with a median survival time of ~13 years, but rare cases with an aggressive course also have been described. Of note, T-LGL should be distinguished from NK-cell leukemia, which does have a fulminant aggressive course (see the section "Aggressive NK-cell leukemia"). In T-LGL, moderate splenomegaly is the most common clinical finding, and lymphadenopathy is rare. Severe neutropenia with or without anemia is common, but thrombocytopenia is rare. A variety of autoimmune disorders, including hemolytic anemia, thrombocytopenia, and pure red blood cell aplasia, also may occur. If treatment is required for cytopenias, immunomodulatory agents such as low-dose methotrexate, cyclosporine A, cyclophosphamide, chlorambucil, or corticosteroids can be effective. Responses can take up to 4 months, and longer therapy often is needed to maintain the response. Purine analogs have been used in the relapsed setting. Splenectomy may be useful in cases with an accompanying splenomegaly, refractory cytopenias, or autoimmune hemolytic anemia or thrombocytopenia. The anti-CD52 monoclonal antibody alemtuzumab can be used in select cases (ORR 50%). There are case reports of long-term remission from LGL leukemia in RA patients treated with rituximab.

Aggressive PTCLs

Adult T-cell leukemia/lymphoma

Adult T-cell lymphoma/leukemia (ATL) is caused by infection with HTLV-1 and occurs in areas of endemic infection (eg, the Caribbean basin and southwestern Japan). The cumulative incidence of adult T-cell lymphoma/leukemia among HTLV-1 carriers is 2.5% in Japan. The virus can be transmitted in breast milk and blood products. The malignant cells have a distinct cloverleaf appearance and are $CD7^-$, and most are $CD4^+/CD8^-$ and $CD25^+$. The following clinical variants have been recognized: (i) acute type with a rapidly progressive clinical course, bone marrow and peripheral blood involvement, hypercalcemia with or without lytic bone lesions, skin rash, generalized lymphadenopathy, hepatosplenomegaly, and pulmonary infiltrates; (ii) lymphoma type with prominent adenopathy but lacking peripheral blood involvement but also associated with an aggressive course; (iii) chronic type with lymphocytosis and occasionally associated with lymphadenopathy, hepatosplenomegaly, and cutaneous lesions but having an indolent course; and (iv) smoldering type with <5% circulating neoplastic cells, skin involvement, and prolonged survival. The chronic and smoldering forms can progress to the acute form after a variable length of time. In the ITLP, 126 patients (9.6% of all PTCLs) were identified with either the acute (13%) or lymphoma-type (87%) ATL. Opportunistic infections are common, and *Strongyloides* serology is recommended before starting therapy.

Survival times in the acute and lymphomatous variants are ~6 and ~10 months, respectively. The median survival time for the chronic form is 2 years. The 4-year OS for the acute, lymphoma, chronic, and smoldering types has been reported to be 5%, 5.7%, 27%, and 63%, respectively. Asymptomatic patients with the smoldering or chronic types can be monitored closely. For young, fit patients with the acute and lymphoma subtypes, the intensive regimen VCAP (vincristine, cyclophosphamide, doxorubicin and prednisolone/AMP [doxorubicin, ranimustine, prednisolone])/VECP (vindesine, etoposide, carboplatin, prednisolone) may be considered. The Japan Clinical Oncology Group (JCOG) reported a phase 3 trial comparing the dose-intensive regimen VCAP/AMP/VECP versus CHOP-14 alone and showed a more favorable CR rate (40% vs 25%, $P = 0.02$) and 3-year

OS (24% vs 13%) that was significant after adjusting for prognostic factors but only for the one-sided *P*-value ($P = 0.028$) (Tsukasaki et al., 2007). The median survival for the intensive regimen was just over 1 year, but toxicity was high (grade 4 neutropenia in 98% and grade 3/4 infections in 32%). Thus, this regimen should be used only in carefully selected patients, particularly with the lymphoma subtype. Relapse rates remain high, and patients should be referred for considered for transplant.

A number of phase 2 studies have evaluated the antiretroviral zidovudine (AZT) and IFN with response rates up to 92% and median OS of 11 months in untreated patients. For the leukemia subtype, these results are superior to what is achieved with combination chemotherapy. For the chronic and smoldering type, a recent meta-analysis demonstrated 100% OS after 10 years with this approach.

Chemokine receptor 4 (CCR4) is expressed in ~90% of cases of ATL. Mogamulizumab (KW-0761) is a humanized monoclonal antibody targeting CC4, and a recently reported phase 2 study demonstrated an ORR of 50%, including eight CRs, in 27 treated patients. The median PFS and OS were 5.2 months and 13.7 months, respectively (Ishida et al., 2012). The most common side effects were lymphopenia (96%), neutropenia (52%) and thrombocytopenia (52%), infusion reaction (89%), and skin rashes (63%). This agent is also be explored in other $CCR4^+$ CTCL and PTCLs.

PTCL, not otherwise specified; systemic anaplastic large cell lymphoma; and angioimmunoblastic T-cell lymphoma

PTCL, not otherwise specified (PTCL-NOS); systemic anaplastic large cell lymphoma (ALCL); and angioimmunoblastic T-cell lymphoma (AILT) are the most common subtypes of PTCL encountered in North America, representing 66% of all PTCL cases.

PTCL-NOS PTCL-NOS is the most common subgroup of PTCLs, accounting for up to 30% of cases worldwide. This is the default PTCL category for any mature T-cell neoplasm that does not fit into any of the specified categories in the WHO classification. Patients typically present with advanced-stage disease, and the 5-year OS is 20%-30% in most series. The morphologic spectrum of PTCL-NOS is wide, including the histiocyte-rich lymphoepithelioid, or Lennert lymphoma. Typically, the neoplastic cells are $CD4^+$/CD8; CD5 and CD7 frequently are downregulated, and ~30% are CD30. Gene expression profiling has been explored in heterogeneous PTCL-NOS to determine whether there are reproducible molecular subsets and to better define prognostic markers within PTCL-NOS. In comparison with B-cell lymphomas, however, large-scale studies are lacking.

Treatment approaches in PTCL have paralleled those DLBCL; as a result, CHOP is considered the standard therapy, despite consistent evidence that it is rarely curative. Furthermore, because of disease rarity, most studies have combined all subtypes that could obscure benefits in select subtypes. Limited analyses suggest that the use of anthracyclines, a key component of CHOP, may not affect outcome in PTCL-NOS (Vose et al., 2008). Although the limitations of CHOP are fully recognized, there is no clear evidence that any other approach is superior.

The DSHNHL group retrospectively analyzed the outcome of PTCL patients ($n = 331$) that had been enrolled in phase 2 or phase 3 aggressive lymphoma studies and evaluated the impact of etoposide. In patients <60 years with a normal LDH, EFS was extended with etoposide ($P = 0.003$), whereas OS did not improve significantly ($P = 0.176$). The addition of etoposide appeared to have the greatest impact in the favorable group of patients with ALK-positive ALCL (3-year EFS 91% vs 82%, $P = 0.012$). In patients with PTCL-NOS, ALK-negative ALCL, and AITL, there was only a trend to improved 3-year EFS (61% vs 48%; $P = 0.057$), with no OS difference observed; however, patient numbers were small. Given that this is not a randomized comparison, the true benefit of the addition of etoposide remains unknown.

Alemtuzumab selectively targets CD52, which is present on normal T-cells but expression across PTCLs is more variable. In the initial studies of alemtuzumab in relapsed or refractory PTCLs, the ORR was 36%, but the TRM was also 36% because of profound immunosuppression and opportunistic infections that can occur. Several studies have evaluated alemtuzumab with CHOP-21 or CHOP-14 in the management of PTCL with variable results. Toxicity has been problematic, including opportunistic infections. Phase 3 studies are ongoing to determine whether the addition of alemtuzumab improves outcome in PTCL.

Pralatrexate is a novel folate analogue that has enhanced uptake and cellular retention compared with MTX. Early studies suggested a sensitivity of TCLs over BCLs. The phase 2 PROPEL study evaluated pralatrexate (with vitamin B_{12} and folate) in relapsed/refractory PTCLs and demonstrated an ORR 29% (CR 11%), a median PFS of 3.5 months and a median DoR of 10.5 months (O'Connor et al., 2011). The main toxicities were mucositis, thrombocytopenia, and neutropenia. These results led to FDA approval of pralatrexate in September 2009 for the treatment of relapsed/refractory PTCL. Studies are ongoing combining pralatrexate with other agents in the up-front and relapsed settings.

Romidepsin is an HDAI that has been evaluated in CTCLs and PTCLs. A phase 2B registration study evaluated romidepsin in 130 patients with relapsed or refractory PTCL. The ORR was 25% (CR 15%), median DoR was 17 months,

and median PFS was 4 months, leading to FDA approval in 2011. Side effects were as previously described in the CTCL studies. A phase 1b study is ongoing combining CHOP with romidepsin for the primary treatment of PTCL.

Belinostat is another HDAI that has demonstrated responses in relapsed or refractory PTCL in a phase 2 trial. Belinostat was granted approval by the FDA for the treatment of patients with PTCL who have received at least one prior therapy. A phase 2 trial (BELIEF trial) of belinostat in 120 patients with PTCL reported overall and complete remission rates of 26% and 11%, respectively, with a median duration of response of 13 months.

CD30 is expressed uniformly in ALCL but also highly restricted, making it an attractive target in this disease. Studies with the nascent anti-$CD30^+$ in relapsed systemic ALCL were largely disappointing, however, and thus to enhance tumor activity an antibody-drug conjugate (ADC), brentuximab vedotin (formerly known as SGN-35), was developed. The ADC conjugates the CD30 monoclonal antibody to the microtubulin inhibitor, monomethyl auristatin E (MMAE), by an enzyme-cleavable dipeptide linker. Following binding to $CD30^+$ and uptake into the cell, MMAE is released and interferes with tubulin formation. A phase 2 study recently was reported in relapsed or refractory systemic ALCL that demonstrated an ORR 86% (CR 57%), median duration of response of 12.6 months, and a median PFS 13.3 months, which also prompted FDA approval for this disease in 2011. The main side effect of brentuximab vedotin is peripheral neuropathy. Studies are ongoing evaluating brentuximab vedotin in the upfront setting with CHP, omitting the vincristine because of overlapping toxicity.

With the disappointing results with CHOP, some groups are evaluating new chemotherapy combinations in PTCL. Gemcitabine has shown reasonable single-agent activity in previously treated patients and is being explored with other agents. Bendamustine has been associated with 50% response rate in relapsed/refractory PTCL. A number of novel agents are under investigation in PTCLs.

Angioimmunoblastic T-cell lymphoma AITL is a well-defined, distinct PTCL subtype, with unique pathobiologic features. Key morphologic findings of AITL include an expanded $CD21^+$ follicular dendritic cell network and prominent arborizing high-endothelial venules (HEV). The neoplastic cells in AITL are mature $CD4^+/CD8^-$ T-cells, expressing most pan-T-cell antigens. EBV-positive B-cells are seen in most cases, and EBV-positive DLBCL has been reported. It appears that the cell of origin is the follicular helper T-cell with T-cells $CD10^+$, $BCL6^+$, and $CXCL13^+$ and derivation also is supported by gene-expression profiling studies.

Patients are typically in their sixth or seventh decade and have advanced-stage disease, often with B-symptoms and hepatosplenomegaly. It was originally believed to be a form of immune dysregulation, with polyclonal gammopathy and other hematologic abnormalities (Coombs-positive hemolytic anemia) reflecting B-cell hyperactivity. Opportunistic infections can occur because of the underlying immunodeficiency.

Survival is similar to PTCL-NOS (5 year ~30%); however, a small proportion may have a more indolent course. CHOP typically is used for the primary therapy, and although the response rate is high, relapse is common and infectious complications are problematic. GELA evaluated AITL patients enrolled on different therapeutic protocols and found no improvement of survival with any therapy, including HDC/ASCT. With the presence of EBV-infected B-immunoblasts and the evidence of B-cell hyperstimulation, GELA also recently evaluated R-CHOP in AITL in a phase 2 study. Of 25 evaluable patients, the ORR was 80% (CR 44%) but with a median follow-up of 2 years, the 2-year PFS was only 42%, which was similar to a prior study using CHOP alone. With poor outcomes using conventional therapy, immunomodulatory agents also have been explored, including cyclosporine, lenolidomide, thalidomide, and interferon. A retrospective study evaluating cyclosporine in relapsed or refractory AITL demonstrated an ORR 67% and a median DoR of 13 months.

Systemic anaplastic large-cell lymphoma ALCL is composed of large $CD30^+$ anaplastic cells with a predilection for a sinusoidal and cohesive growth pattern. In the WHO classification, primary systemic ALCL is separated from cutaneous ALCL; and more recently, ALK-positive ALCL has been defined as a distinct entity (Table 21-3). Cases of ALK-positive ALCL are associated with a characteristic chromosomal translocation, t(2;5)(p23;q35), resulting in a fusion gene, *NPM-ALK*, encoding a chimeric protein with tyrosine kinase activity. With the availability of antibodies to the ALK protein, ALK expression can be demonstrated in 60%-85% of all systemic ALCL, with higher frequencies seen in the pediatric and young adult age-groups. In contrast, although ALK-negative ALCL lacks any defining features, there is accumulating evidence that it should be separated from other PTCLs; as a result, it is considered a provisional entity in the updated WHO classification.

ALK-positive ALCL Morphologically ALK-positive ALCL has pathognomonic "hallmark cells" recognized by their eccentric, horseshoe, or kidney-shaped nuclei. In addition to strong expression of CD30, ALK-positive ALCL is usually positive for epithelial membrane antigen (EMA) and cytotoxic markers (TIA1, granzyme B, and perforin). Several studies have established that patients with ALK-positive ALCL have a more favorable prognosis with

anthracycline-based chemotherapy than patients who have ALK-negative ALCL and other PTCLs, as well as DLBCL, at least in the prerituximab treatment era. The improved outcome in part is related to the young age at presentation. The international T-cell lymphoma project (ITLP) confirmed the superior outcome of ALK-positive ALCL (5-year FFS 60%; 5-year OS 60%) compared with ALK-negative ALCL (5-year FFS 36%; 5-year OS 49%). If the comparison is confined to patient's <40 years old, however, there was no difference in survival. Similar findings were reported from a retrospective analysis of patients with ALCL enrolled on GELA studies, which reported that in patients <40 years of age, there was no impact of ALK status on PFS or OS (Sibon et al., 2012).

Given the favorable outcome with anthracycline-based chemotherapy, CHOP is considered to be the standard therapy of ALK-positive ALCL. Patients with multiple IPI factors have a poor outcome, however, and could be considered for clinical trials. Given the strong and uniform expression of CD30, the ADC brentuximab vedotin has been tested in the relapsed or refractory setting and has significant efficacy, prompting evaluation in the frontline setting.

Crizotinib is a small molecule inhibitor of the ALK tyrosine kinase that has demonstrated activity in a subset of patients with ALK positive nonsmall-cell lung cancer. Several case reports of patients with multiply relapsed ALK positive anaplastic large cell lymphoma (ALCL) reported complete responses after treatment with crizotinib.

ALK-negative ALCL Patients with ALK-negative ALCL tend to be older at presentation; the clinical presentation is similar to ALK-positive cases, but sites of extranodal disease may vary. Pathologically, it is not reproducibly distinguished from ALK-positive ALCL other than lacking the ALK protein. ALK-negative ALCL has been difficult to define, in part due to a lack of uniformly applied diagnostic criteria across studies. Recently, a recurrent balanced translocation t(6;7)(p25.3;q32.3) has been identified in ALK-negative ALCL, but the significance is unknown. Previously, it was argued that ALK-negative ALCL had a similar outcome to PTCL-NOS and they should be grouped together. In recent years, there is accumulating evidence that they differ not only pathologically and genetically but also prognostically. The ITLP compared the outcome of ALK-negative ALCL with PTCL-NOS and established that ALK-negative ALCL had a more favorable 5-year FFS (36% vs 20%, $P = 0.012$) and OS (49% vs 32%, $P = 0.032$). These data confirm that ALK-negative ALCL should be considered distinct from both ALK-positive ALCL and PTCL-NOS. Although the survival is more favorable than PTCL-NOS, it is still poor, particularly with multiple IPI factors. Novel therapies, including brentuximab vedotin, are being explored.

ALK-negative ALCL associated with breast implants ALCL associated with implants typically involves the capsule without invasion of the breast tissue, or it presents as an unexplained seroma or mass, which usually is $CD30^+$ ALK negative. The neoplastic cells float in the effusion fluid or become embedded tissue; importantly, however, breast parenchyma usually is not involved and the ALCL cells are at distance from the breast tissue. It is associated with both silicone and saline implants. Recently, investigators at the University of Southern California have collected 90 cases to date worldwide and put forth recommendations (Brody et al., 2012). A total capsulectomy should be performed, and because bilateral cases have been reported, removal of the uninvolved breast implant should be considered. The growing body of literature supports that ALK-negative ALCL in this setting appears to have a more indolent clinical course, and most patients can be observed following removal of the implant and capsule. Recent reports suggest similar survival compared with those who received chemotherapy or radiation, but rare aggressive cases have been reported. Cases that have identified a distinct breast mass may be better classified as a typical systemic ALK-negative ALCL and may be treated accordingly (Aladily et al., 2012).

Extranodal NK-/T-cell lymphoma, nasal type

Extranodal NK-/T-cell lymphomas, nasal type, display great variation in racial and geographic distribution, with the majority of cases occurring in the Far East. Patients are typically males, 40-50 years old. The tumor cells show angioinvasion and necrosis is prominent. The designation NK/T is used to reflect the fact that although most are NK-cell derived ($CD2^+$, $CD56^+$, CD3 [cytoplasmic]$^+$, EBV^+), rare cases with identical clinical and cytologic features exhibit an EBV-positive or $CD56^-$, cytotoxic T-cell marker positive (TIA1, perforin, and granzyme B). Circulating EBV in the peripheral blood can often be detected, providing another method of disease monitoring. The majority of cases remain localized with <20% presenting with advanced-stage disease. Despite the predominant nasal location, spread to the CSF is uncommon. Most occur in the nasal region, but identical tumors also can occur at extranasal sites, such as the skin, soft tissue, GI tract, and testis (ie, extranasal). It appears that cases involving extranasal regions may have a more aggressive course. From the ITLP the 5-year OS for stage I/II NK-/T-cell lymphomas was ~50% and 15% for nasal and extranasal sites, respectively, and the corresponding estimates for stage III/IV patients were 30% and <10%. The IPI does not stratify patients well because most have localized disease and often with good PS. A Korean index using B symptoms, stage (I/II vs III/IV), regional lymph nodes, LDH, and PS appears to be more useful in prognostication,

particularly for the low and low-intermediate IPI cases and may help to guide treatment decisions. Patients fall into four risk groups with widely disparate outcomes: group 1: no RF, 5-year OS ~ 81%; group 2: 1 RF, 5-year OS ~64%; group 3: 2 RF, 5-year OS ~34%; and group 4: 3 or 4 RF, 5-year OS 7%. Risk factors identified in other studies have also included local tumor invasion (tone or skin), high Ki-67, or EBV DNA titer >6.1×10^7 copies/mL.

Accumulating evidence indicates radiotherapy is important in the management of patients with localized NK-/T-cell lymphoma with more favorable outcomes observed using high doses of radiotherapy (50-60 Gy) early in the frontline setting. Recently, the use of platinum as a radiosensitizer has been explored and may allow for the use of lower, less-toxic doses of radiation. Furthermore, because systemic relapse can occur with single-modality radiotherapy, other novel combinations are being tested. The outcome with CHOP has been disappointing, and it has been speculated that this may be due to overexpression of p-glycoprotein expression conferring multidrug resistance. Concurrent radiation (40 Gy) and cisplatin, followed by three cycles of VIPD (etoposide, ifosfamide, cisplatin), was evaluated in stage IE/IIE nasal NK-/T-cell lymphoma. In this highly selected population, the CR rate was 83% and the 3-year PFS was 85% (Kim et al., 2009). Similarly, concurrent radiotherapy (50 Gy) and DeVIC chemotherapy (dexamethasone, etoposide, ifosfamide, carboplatin) was evaluated in a phase 1/2 trial in localized nasal NK-/T-cell lymphoma with good results (CR 77%, 2-year PFS 67%) (Yamaguchi et al., 2009). In the absence of a randomized trial, the most recent NCCN guidelines suggest either high-dose radiotherapy alone (>50 Gy) for stage 1 patients without risk factors (as described) or concurrent chemoradiotherapy (stage 1 or 2) using either of the noted regimens for localized NK-/T-cell lymphoma.

For advanced-stage disease, L-asparaginase has emerged as an active agent in NK-/T-cell lymphomas with an ORR of 87% (CR 50%) in relapsed or refractory patients. Antithrombin levels require close monitoring. A phase 2 study evaluating L-asparaginase in combination with MTX and dexamethasone (AspaMetDex) in previously treated patients, demonstrates an ORR of 78% (CR 61%) and a median DoR of 12 months (Jaccard et al., 2011). A phase 2 study evaluating the SMILE regimen (steroid, methotrexate, ifosfamide, L-asparaginase, etoposide) in 38 patients with either newly diagnosed stage IV or relapsed or refractory NK-/T-cell lymphoma demonstrated an ORR after two cycles of 79% (CR 45%) and 19 patients subsequently underwent SCT. The 1-year OS rate was 55%, but grade 4 neutropenia occurred in 92% and the grade 3/4 infection rate was 61%. Additional studies incorporating L-asparaginase in the frontline treatment of both localized and advanced-stage NK-/T-cell lymphoma are ongoing.

Aggressive NK-cell leukemia

Aggressive NK-cell leukemia is a rare form of leukemia that almost always is associated with EBV infection and has a median survival of only 3 months. It is seen most often in Asians, and the median age of onset is 42 years. Typically, the bone marrow and peripheral blood are involved in addition to the liver and spleen. Patients often have fever and constitutional symptoms and multiorgan failure with coagulopathy and hemophagocytic syndrome. It is unclear whether aggressive NK-cell leukemia represents the leukemic phase of extranodal NK-/T-cell lymphoma. There is no known curative therapy, and responses to chemotherapy are usually brief. Some encouraging results have been seen with L-asparaginase–based treatment in this disease and extranodal NK-/T-cell lymphoma but both require further study.

Rare aggressive PTCL subtypes

Subcutaneous panniculitis-like T-cell lymphoma Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL) is an extremely uncommon PTCL subtype that preferentially infiltrates the subcutaneous tissue. It has been determined that tumors with γδ phenotype have a far inferior prognosis to those with αβ phenotype (5-year OS, 11% for γδ vs 82% for αβ) (Willemze et al., 2008). In the WHO classification, SCPTCL is confined only to the αβ, which usually have a $CD4^-$/ $CD8^+$, and $CD5^-$ phenotype. Cases with a γδ phenotype are combined in a new, rare PTCL entity, termed *primary cutaneous γδ T-cell lymphoma* (see section "Primary cutaneous PTCL, rare aggressive subtypes") because of similar aggressive behavior. The optimal therapy for αβ SCPTCL is unknown, with durable responses observed with both CHOP and immunosuppressive agents.

Hepatosplenic T-cell lymphoma Hepatosplenic T-cell lymphoma is a rare PTCL subtype occurring usually in young men (median age 34 years) presenting with hepatosplenomegaly and bone marrow involvement. Up to 20% of hepatosplenic T-cell lymphomas occur in the setting of immunosuppression, most commonly following solid organ transplantation. It also has been observed in patients treated with azathioprine and the TNFα inhibitor, infliximab, which is used in Crohn disease. The splenic red pulp is diffusely involved, and the liver will show a sinusoidal pattern. Most tumor cells are $CD3^+$, $CD4^-$, and $CD8^-$, and most are associated with isochrome 7q. The majority of cases are of the γδ TCR type; however, rare cases that are of the αβ TCR type have been reported. The prognosis is extremely poor with rare long-term survivors. The optimal therapy is unknown; however, CHOP does not appear to cure this disease. Long-term survivors have been reported with high-dose chemotherapy and ASCT or alloSCT and referral at diagnosis is suggested.

Enteropathy-associated T-cell lymphoma Enteropathy-associated T-cell lymphoma (EATL) is a rare, aggressive intestinal tumor with a male predominance that often occurs in the setting of celiac disease. It most commonly involves the jejunum or ileum. Patients often present with abdominal pain, and intestinal perforation can occur. The prognosis is extremely poor due to chemotherapy resistance and difficult treatment delivery related to abdominal complications that can arise in the setting of malabsorption. In some cases, there is a childhood history of celiac disease, but more commonly, the disease occurs in adulthood. Alternatively, there is a prodrome of refractory disease or a concomitant diagnosis of celiac disease is found at the time the lymphoma is discovered. In the updated WHO classification, a sporadic, monomorphic variant, type II EATL, has been defined that occurs in 10%-20% of cases and has a broader geographic distribution that includes Asia. An association with celiac disease has not been definitively proven in this subtype; thus, this may represent a distinct disease entity. In the common subtype, the neoplastic cells are $CD3^+$, $CD7^+$, $CD4^-$, $CD8^{-/+}$, $CD56^-$ and contain cytotoxic proteins. The monomorphic form is $CD3^+$, $CD4^-$, $CD8^+$, and $CD56^+$.

The ITLP recently reported on 62 patients with EATL, which represented 5.4% of all lymphomas worldwide, most commonly in Europe. Type I and type II EATL represented 66% and 34% of the cases, respectively. The 5-year FFS was only 4% and OS was 20%, with the majority of patients treated with CHOP-type chemotherapy. Similar disappointing results are observed in other studies with CHOP-type therapy, which has prompted evaluation of HDC/ASCT (see "Transplant in PTCL").

Primary cutaneous PTCL, rare aggressive subtypes

Primary cutaneous γδ T-cell lymphoma In the updated WHO classification, primary cutaneous γδ T-cell lymphoma is now considered a distinct entity, which also includes cases previously known as SCPTCL with a γδ phenotype, as described earlier. Clinically, the extremities are commonly affected, and the presentation can be variable, with patch or plaque disease or subcutaneous and deep dermal tumors that may exhibit necrosis and ulceration. The clonal T-cells have an activated γδ cytotoxic phenotype and most are $CD4^-/CD8^-$. Prognosis is poor in this disease, particularly with subcutaneous fat involvement, with a fulminant clinical course and chemoresistance.

Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma This provisional entity typically presents with generalized cutaneous lesions appearing as eruptive papules, nodules, and tumors with central ulceration and necrosis. Histologically, there is marked epidermotropism, and invasion into the dermis and adnexal structures is common. The tumor cells are $CD3^+$, $CD4^-$, $CD8^+$, and cytotoxic marker positive, and the clinical course is aggressive.

Transplant in PTCL

Multiple retrospective studies have been published evaluating the impact of upfront transplantation in PTCL, as has been comprehensively reviewed (Yared et al., 2012). Trial interpretation and comparisons are difficult for a number of reasons, including the evaluation of heterogeneous patient populations, potential for selection bias, and the dearth of intention-to-treat (ITT) data. Because there are no reported prospective randomized phase 3 trials comparing HDC/ASCT with conventional-dose chemotherapy, specifically for PTCL, it remains challenging to determine the relative impact of patient selection versus true differences in efficacy.

GELA performed a retrospective analysis of the impact of upfront autologous transplant in T-cell lymphomas. Limiting the study to patients who achieved CR, a matched-pair analysis was performed comparing dose-intensive chemotherapy alone (ACVB or NCVB (mitoxantrone substitution) versus chemotherapy plus HDC/ASCT. No difference in DFS or OS was found, but the ACVB is considered more dose-intensive than CHOP.

Several phase 2 prospective studies of upfront transplant have been published and represent more homogeneous populations of treated patients. The Nordic group completed the largest prospective phase 2 trial of upfront transplant (NLG-T-01) in 160 patients with PTCL, excluding ALK-positive ALCL. The planned treatment scheduled was CHOEP-14 for six cycles (CHOP-14 in patients >60 years), followed by BEAM/BEAC and ASCT in responding patients (d'Amore et al., 2012). In total 160 patients represented the ITT population. Most patients had good functional status (71% with PS scores of 0 or 1), but 72% had an IPI score of >2. The CR rate pretransplant was 81% to transplant, and the overall transplant rate was 70% with a TRM of 4%. With median follow-up of 5-years, the 5-year PFS was 44% and 5-year OS was 51%. Patients with ALK-negative ALCL appeared to have a superior 5-year PFS (61%) compared with PTCL-NOS (38%), EATL (38%), or AILT (49%), but this was not statistically significant. The 5-year OS for patients who underwent transplant was 61% compared with 28% in those who did not. These results suggest that this approach may be appropriate in select patients but still represent level 2 evidence given the absence of data from a phase 3 trial.

In eligible patients, HDC/ASCT represents the standard of care for relapsed or refractory PTCL. In the original PARMA study in which HDC/ASCT emerged as superior to second-line chemotherapy alone in relapsed aggressive NHL, immunophenotyping was not routinely performed. A subsequent report of prognostic factors did not identify a difference in

outcome in B- versus T-cell lymphomas; however, the number of patients with PTCLs was small. There has been no similar randomized study in PTCLs, but a number of retrospective studies report a salvage rate in this setting ranging from 18% to 60% (Yared et al., 2012). Given the overall body of evidence, ASCT frequently is offered to patients with PTCL with relapsed, chemosensitive disease.

AlloSCT, with either myeloablative or RIC, also has been reported to yield durable remission in many cases (3-year EFS 23%-64%). Evidence supporting a graft-versus-PTCL effect comes from studies with donor lymphocyte infusions. The largest study published to date evaluated 77 previously treated patients with mainly myeloablative conditioning (74%). The 5-year PFS was 53%, but the TRM was 34% at 5 years. A phase 2 trial evaluating RIC and alloSCT in 17 patients, demonstrated a 3-year PFS of 64% with a TRM of 6%. Allogeneic transplantation is promising in the treatment of PTCL, but it is limited by the availability of stem cell donors and toxicity related to graft-versus-host disease.

Novel PTCL therapies

A number of agents are being explored in PTCL, three of which have FDA approval for use today in relapsed/refractory disease. Pralatrexate is a novel folate analogue that has enhanced uptake and cellular retention compared with MTX. Early studies suggested a sensitivity of TCLs over BCLs. The phase 2 PROPEL study evaluated pralatrexate (with vitamin B_{12} and folate) in relapsed/refractory PTCLs and demonstrated an ORR 29% (CR 11%), a median PFS of 3.5 months and a median DoR of 10.5 months (O'Connor et al., 2011). The main toxicities were mucositis, thrombocytopenia and neutropenia. These results led to FDA approval of pralatrexate in September 2009 for the treatment of relapsed/refractory PTCL. Studies are ongoing combining pralatrexate with other agents in the up-front and relapsed settings.

As described previously, romidepsin is a HDAIs that has been evaluated in CTCLs and PTCLs. A phase 2B registration study was published evaluating romidepsin in 130 patients with relapsed or refractory PTCL. The ORR was 25% (CR 15%), median DoR was 17 months, and median PFS was 4 months, leading to FDA approval in 2011. Belinostat, another HDAC inhibitor, was FDA approved for R/R PTCL in 2014 and demonstrates similar activity to romidepsin. Alisertib is an aurora kinase inhibitor which has demonstrates meaningful single agent activity in R/R PTCL and is under ongoing study.

CD30 is expressed uniformly in ALCL but is also highly restricted to neoplastic cells, making it an attractive target in this disease. Studies are ongoing evaluating brentuximab vedotin in the upfront setting with CHP, omitting the vincristine because of overlapping toxicity.

Key points

- BL should be treated with dose-intensive regimens as R-CHOP is inadequate. The treatment should include CNS prophylaxis.
- Patients with congenital or acquired immunodeficiency have an increased risk of lymphoma and often respond poorly to therapy.
- PTCLs have an inferior outcome to DLBCL. The exception is ALK-positive ALCL, which has a high cure rate with CHOP chemotherapy unless multiple IPI factors are present at diagnosis.

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