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113 Non-Hodgkin’s Lymphoma

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Non-Hodgkin’s

Lymphoma Non-Hodgkin’s lymphomas (NHLs) are cancers of mature B, T, and natural killer (NK) cells. They were distinguished from Hodgkin’s lym phoma (HL) upon recognition of the Reed-Sternberg (RS) cell and dif fer from HL with respect to their biologic and clinical characteristics. Whereas ~80–85% of patients with HL will be cured of their lymphoma by chemotherapy with or without radiotherapy, the prognosis and natural history of NHL tend to be more variable. NHL can be classi fied as either a mature B-NHL or a mature T/NK-NHL depending on whether the cancerous lymphocyte is a B, T, or NK cell, respectively. Within each category are lymphomas that grow quickly and behave aggressively, as well as lymphomas that are more indolent, or slow growing, in nature. For a list of the World Health Organization (WHO) classification of lymphoid neoplasms, see Table 113-1. ■ ■EPIDEMIOLOGY AND ETIOLOGY In 2023, it is estimated that there will be 80,550 new cases of NHL in the United States, ~4% of all new cancers in both males and females, making it the seventh most common cause of cancer-related death in both women and men. The incidence is nearly 10 times the incidence TABLE 113-1 WHO-HAEM5 Classification of Lymphoid Malignancies B CELL T CELL Mature (peripheral) B-cell neoplasms Mature (peripheral) T-cell neoplasms Lymphoplasmacytic lymphoma T-cell granular lymphocytic leukemia (Waldenström’s macroglobulinemia) Hairy cell leukemia Splenic marginal zone B-cell Adult T-cell leukemia/lymphoma (HTLV-1+) Extranodal NK/T-cell lymphoma, lymphoma Extranodal marginal zone B-cell nasal type Enteropathy-associated T-cell lymphoma of MALT type Nodal marginal zone B-cell lymphoma Hepatosplenic T-cell lymphoma lymphoma Follicular lymphoma Mantle cell lymphoma Diffuse large B-cell lymphoma Subcutaneous panniculitis-like T-cell lymphoma Mycosis fungoides Sezary syndrome (including subtypes) High-grade B-cell lymphoma with Peripheral T-cell lymphoma NOS MYC and BCL2 rearrangements High-grade B-cell lymphoma NOS High-grade B-cell lymphoma with Angioimmunoblastic T-cell lymphoma Anaplastic large-cell lymphoma, ALK+ 11q aberrations Burkitt’s lymphoma/Burkitt’s cell Anaplastic large-cell lymphoma, ALK– leukemia Primary mediastinal large B-cell lymphoma Mediastinal grey zone lymphoma Primary large B-cell lymphoma of immune-privileged sites Plasmablastic lymphoma Primary effusion lymphoma HHV8+ DLBCL NOS Intravascular large B-cell lymphoma ALK+ large B-cell lymphoma Abbreviations: DLBCL, diffuse large B-cell lymphoma; HHV, human herpesvirus; HTLV, human T-cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer; NOS, not

otherwise specified; WHO, World Health Organization. Source: Adapted from R Alaggio et al: The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 36:1720, 2022.

of HL. There is a slight male-to-female predominance and a higher incidence for Caucasians than for African Americans. The incidence rises steadily with age, especially after age 40, but lymphomas are also among the most common malignancies in adolescent and young adult patients. The incidence of NHL has nearly doubled over the past 20–40 years and continues to rise by 1.5–2% each year. Patients with both primary and secondary immunodeficiency states are predisposed to developing NHL. These include patients with HIV infection, patients who have undergone organ transplantation, and patients with inherited immune deficiencies and autoimmune conditions. The 5-year survival rate for NHL is 74% and is higher for Caucasians than it is for African Americans.

The incidence of NHL and the patterns of expression of the various subtypes differ geographically and across age groups. T-cell lympho mas are more common in Asia than in Western countries, whereas certain subtypes of B-cell lymphomas such as follicular lymphoma (FL) are more common in Western countries. A specific subtype of NHL known as the angiocentric nasal T/NK-cell lymphoma has a striking geographic occurrence, being most frequent in southern Asia and parts of Latin America. Another subtype of NHL associated with infection by human T-cell lymphotropic virus (HTLV) 1 is seen particularly in southern Japan and the Caribbean (see Chap. 207). Likewise, there are differences in the age-dependent incidence of NHL by histologic subtype, with aggressive lymphomas like diffuse large B-cell lymphoma (DLBCL) and Burkitt’s lymphoma (BL) being the most common enti ties in children, and DLBCL and indolent lymphomas including FL being the most common forms in adults. The relative frequencies of the various types of lymphoid malignancies, including HL, plasma cell disorders, and lymphoid leukemias, are shown in Fig. 113-1. CHAPTER 113 Non-Hodgkin’s Lymphoma A number of environmental factors have been implicated in the occurrence of NHL, including infectious agents, chemical exposures, and medical treatments. Several studies have demonstrated an associa tion between exposure to agricultural chemicals and an increased inci dence of NHL. Patients treated for HL can develop NHL; it is unclear whether this is a consequence of the HL or its treatment, especially radiation. Several NHLs are associated with infectious agents (Table 113-2). Epstein-Barr virus (EBV) is associated with the development of BL in Central Africa and the occurrence of aggressive NHL in immuno suppressed patients in Western countries. The majority of primary central nervous system (CNS) lymphomas are associated with EBV. EBV infection is strongly associated with the occurrence of extrano dal nasal NK/T-cell lymphomas in Asia and South America. HTLV-1 infects T cells and leads directly to the development of adult T-cell lymphoma (ATL) in a small percentage of patients infected as babies through ingestion of breast milk of infected mothers. The median age of patients with ATL is ~56 years; thus, HTLV-1 demonstrates a long latency from infection to oncogenesis (Chap. 207). Infection with HIV predisposes to the development of aggressive B-cell NHL. This may be through overexpression of interleukin 6 by infected macrophages. Infection of the stomach by the bacterium Helicobacter pylori induces the development of gastric mucosa-associated lymphoid tissue (MALT) lymphomas. This association is supported by evidence that patients treated with antibiotics to eradicate H. pylori have regression of their MALT lymphoma. The bacterium does not transform lymphocytes to produce the lymphoma; instead, a vigorous immune response is made to the bacterium, and the chronic antigenic stimulation leads to the neoplasia. MALT lymphomas of the skin may be related

to Borrelia species infections in Europe, those of the eyes to Chlamydophila psit taci, and those of the small intestine to Campylobacter jejuni. Chronic hepatitis C virus infection has been associated with the development of lymphoplasmacytic lymphoma and splenic marginal zone lymphoma (MZL). Human herpesvirus 8 is associated with primary effusion lym phoma in HIV-infected persons and multicentric Castleman's disease, a diffuse lymphadenopathy associated with systemic symptoms of fever, malaise, and weight loss. In addition to infectious agents, a number of other diseases or expo sures may predispose to developing lymphoma (Table 113-3). Diseases of inherited and acquired immunodeficiency as well as autoimmune

Plasma cell disorders 16% CLL 9% Non-Hodgkin's lymphoma 62.4% Hodgkin's disease 8.2% ALL 3.8% PART 4 Oncology and Hematology FIGURE 113-1 Relative frequency of lymphoid malignancies. ALL, acute lymphoid leukemia; CLL, chronic lymphocytic leukemia; MALT, mucosa-associated lymphoid tissue. diseases are associated with an increased incidence of lymphoma. The association between immunosuppression and induction of NHLs is compelling because if the immunosuppression can be reversed, a percentage of these lymphomas regress spontaneously. The incidence of NHL is nearly a hundredfold increased for patients undergoing organ transplantation necessitating chronic immunosuppression and is greatest in the first year posttransplant. About 30% of these arise as a polyclonal B-cell proliferation that evolves into a clonal B-cell malignancy. The NHLs that occur in the context of immunosuppres sion or immunodeficiency, including HIV infection, are frequently associated with EBV. Histologically, DLBCLs are most frequently asso ciated with immunosuppression and autoimmune diseases, although almost all histologies can be seen, especially MALT lymphomas in the context of autoimmune diseases such as Sjögren's syndrome and Hashimoto's thyroiditis. The rare inherited immunodeficiency diseases X-linked lymphoproliferative syndrome, Wiskott-Aldrich syndrome, Chédiak-Higashi syndrome, ataxia-telangiectasia, and common vari able immunodeficiency syndrome are complicated by highly aggressive TABLE 113-2 Infectious Agents Associated with the Development of Lymphoid Malignancies INFECTIOUS AGENT LYMPHOID MALIGNANCY Epstein-Barr virus Burkitt's lymphoma Post–organ transplant lymphoma Primary CNS diffuse large B-cell lymphoma Hodgkin's lymphoma Extranodal NK/T-cell lymphoma, nasal type HTLV-1 Adult T-cell leukemia/lymphoma HIV Diffuse large B-cell lymphoma Burkitt's lymphoma Hepatitis C virus Lymphoplasmacytic lymphoma Helicobacter pylori Gastric MALT lymphoma Human herpesvirus 8 Primary effusion lymphoma Multicentric Castleman's disease Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

Non-Hodgkin's lymphoma subtypes 31% Diffuse large B-cell lymphoma 22% Follicular lymphoma 7.6% MALT lymphoma 7.6% Mature T-cell lymphoma 6.7% Small lymphocytic lymphoma 6% Mantle cell lymphoma 2.4% Mediastinal large B-cell lymphoma 2.4% Anaplastic large-cell lymphoma 2.4% Burkitt's lymphoma 1.8% Nodal marginal zone lymphoma 1.7% Precursor T-lymphoblastic lymphoma 1.2% Lymphoplasmacytic lymphoma 7.4% Others lymphomas. The elevated incidence of lymphoma in iatrogenic immu nosuppression, AIDS, and autoimmune disease argues strongly for immune dysregulation contributing to the pathogenesis of some lym phomas. An increased risk of NHL has been observed in first-degree relatives with NHL, HL, or chronic lymphocytic leukemia (CLL). In large database studies, ~9% of patients with lymphoma or CLL have a first-degree relative with a lymphoproliferative disorder. ■ ■IMMUNOLOGY All lymphoid cells are derived from a common hematopoietic pro genitor that gives rise to lymphoid, myeloid, erythroid, monocyte, and

megakaryocyte lineages. Through the ordered and sequential activa tion of a series of transcription factors, the cell first becomes commit ted to the lymphoid lineage and then gives rise to B and T cells. About 90% of all lymphomas are of B-cell origin. A cell becomes committed to B-cell development when it expresses the master B lin eage transcription factor PAX5, which ultimately results in a transcrip tional program that leads to the rearrangement of its immunoglobulin genes, which involves chromosomal recombination as well as somatic hypermutation to create an immunoglobulin gene that is unique to that B cell. The sequence of cellular changes, including changes in TABLE 113-3 Diseases or Exposures Associated with Increased Risk of Development of Malignant Lymphoma Inherited immunodeficiency disease Klinefelter's syndrome Chédiak-Higashi syndrome Ataxia-telangiectasia syndrome Wiskott-Aldrich syndrome Common variable immunodeficiency Autoimmune disease Sjögren's syndrome Celiac sprue Rheumatoid arthritis and systemic lupus erythematosus Chemical or drug exposures Phenytoin Dioxin, phenoxy herbicides Radiation Prior chemotherapy and radiation disease Acquired immunodeficiency diseases Iatrogenic immunosuppression HIV-1 infection Acquired hypogammaglobulinemia therapy Anti-TNF drugs Abbreviations: HIV, human immunodeficiency virus; TNF, tumor necrosis factor.

Bone marrow Pre–B ALL Unclassified ALL TdT HCR κR or D TdT TdT HCR HCR λR or D H H HLA–DR+ CD19+ HLA–DR+ HLA–DR+ CD19+ CD19+ CD10+ CD10+ CD20+ CD22+ Lymphoid stem cell Early B cells Intermediate B cells Mature B cells Antigen-independent differentiation Antigen-driven differentiation FIGURE 113-2 Pathway of normal B-cell differentiation and relationship to B-cell lymphomas. HLA-DR, CD10, CD19, CD20, CD21, CD22, CD5, and CD38 are cell markers used to distinguish stages of development. Terminal transferase (TdT) is a cellular enzyme. Immunoglobulin heavy chain gene rearrangement (HCR) and light chain gene rearrangement or deletion (κR or D, λR or D) occur early in B-cell development. The approximate normal stage of differentiation associated with particular lymphomas is shown. ALL, acute lymphoid leukemia; CLL, chronic lymphocytic leukemia; SL, small lymphocytic lymphoma. cell-surface phenotype that characterizes normal B-cell development, is shown in Fig. 113-2. Most B-cell lymphomas arise following the process of immunoglobulin gene recombination and somatic hyper mutation, which leads to class switching and affinity maturation of the mature immunoglobulin, respectively, suggesting that it is the errorprone nature of these genetic events that contributes to oncogenesis. Certainly the frequency of chromosomal translocations that result in the activation of an oncogene or the inactivation of a tumor-suppressor gene in B-cell NHL may be the result of these normal cellular processes gone awry (see below). In addition, the key roles of the transcription factors MYC and BCL6 and the antiapoptotic protein BCL2 in the process of B-cell development explain why the genes encoding these proteins are commonly mutated in B-cell lymphomas. A cell becomes committed to T-cell differentiation upon migration to the thymus and rearrangement of T-cell receptor (TCR) genes. This requires the expression of the T-cell master regulatory transcription factor, NOTCH-1. As in B cells, the development of the mature TCR involves the rearrangement and recombination of the TCR loci, which is error-prone and potentially oncogenic. The sequence of the events that characterize T-cell development is depicted in Fig. 113-3. Although lymphoid malignancies often retain the cell-surface phenotype of lymphoid cells at particular stages of differentiation, this information is of little clinical or prognostic consequence. The so-called stage of differentiation of a malignant lymphoma does not predict its natural history. The antigen footprint, or immunopheno type, of the cell, however, is valuable diagnostically as it allows for the distinguishing of specific NHL subtypes. It can be detected by flow

Follicular/diffuse IgM±IgG or IgG lymphomas Burkitt’s Lymphoid follicle HLA–DR+ IgM IgM IgM CD19+/− CD20+ IgD IgG CD22+/− CD21+/− Follicular center B cells Multiple myeloma HLA–DR+ HLA–DR+ HLA–DR+ Waldenström’s CD19+ CD19+ CD19+ IgM CD20+ CD20+ CD20+ CD22+ CD22+ CD22+ CD21+ CD21+ CD21+ Mantle cell lymphoma CLL SL CD19+/− CD38+ CD20+ PCA–1+ IgM±IgD IgM IgD CD38+ CHAPTER 113 Secretory B cells HLA–DR+ HLA–DR+ CD19+ CD19+ Non-Hodgkin’s Lymphoma CD10+/− CD20+ CD20+ CD22+/− CD22+ CD21+ CD21+ CD5+ CD5+ Mantle zone B cells cytometry of single-cell suspension from blood, bone marrow, body fluid, or disaggregated tissue using fluorescently labeled antibodies against these antigens or by immunohistochemical staining of paraffinembedded tissue sections with enzyme-linked antibodies against these antigens followed by a colorimetric reaction. As already mentioned, malignancies of lymphoid cells are associated with recurring genetic abnormalities including chromosomal translo cations and genetic mutations that may in part be the result of aberrant immunoglobulin or TCR development. While specific genetic abnor malities have not been identified for all subtypes of lymphoid malig nancies, it is presumed that they exist. As previously discussed, B cells are even more susceptible to acquiring mutations during their matura tion in germinal centers; the generation of antibody of higher affinity requires the introduction of mutations into the variable region genes in the germinal centers. Given this, other nonimmunoglobulin genes, e.g., bcl-6, may acquire mutations as well. Likewise, many lymphomas con tain balanced chromosomal translocations involving the antigen recep tor genes; immunoglobulin genes on chromosomes 2, 14, and 22 in B cells; and T-cell antigen receptor genes on chromosomes 7 and 14 in T cells. The rearrangement of chromosome segments to generate mature antigen receptors must create a site of vulnerability to aberrant recom bination. Examples of this type of event include the (8;14)(q24;q32) translocation in BL, involving the MYC proto-oncogene and the IgH gene; the (14;18)(q32;q32) translocation in FL, involving the BCL2 proto-oncogene and the IgH gene; and the (11;14) (q13;q32) translo cation in mantle cell lymphoma (MCL), involving the gene encoding cyclin D1 (CCDN1) and the IgH gene. Less commonly, chromosomal

T-CELL DIFFERENTIATION T-CELL MALIGNANCIES THYMUS Stage I Prothymocyte Majority of T-cell ALL CD: 2, 7, 38, 71 Stage II Thymocyte Minority of T-ALL Majority of T-LL CD: 1, 2, 4, 7, 8, 38 Stage III Thymocyte Minority of T-LL Rare T-ALL CD: 2, 3, 4/8, 5, 6, 7; TCR PERIPHERAL BLOOD AND NODES Majority of T-CLL, CTCL, Sezary Cell, NHL Mature T Helper Cell CD: 2, 3, 4, 5, 6, 7; TCR PART 4 Oncology and Hematology Mature T Cytotoxic/ Suppressor Cell Minority of T-CLL, NHL CD: 2, 3, 5, 6, 7, 8; TCR FIGURE 113-3 Pathway of normal T-cell differentiation and relationship to T-cell lymphomas. CD1, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD38, and CD71 are cell markers used to distinguish stages of development. T-cell antigen receptors (TCR) rearrange in the thymus, and mature T cells emigrate to nodes and peripheral blood. ALL, acute lymphoid leukemia; CTCL, cutaneous T-cell lymphoma; NHL, nonHodgkin’s lymphoma; T-ALL, T-cell ALL; T-CLL, T-cell chronic lymphocytic leukemia; T-LL, T-cell lymphoblastic lymphoma. translocations produce fusion genes that encode chimeric oncogenic proteins. Examples of this include the (2;5)(p23;q35) translocation involving the ALK and NPM1 genes in anaplastic large-cell lymphoma (ALCL) and the t(11;18)(q21;q21) translocation involving the API2 and MLT genes in MALT lymphoma. Table 113-4 presents the most common translocations and associated oncogenes for various subtypes of lymphoid malignancies. Gene profiling using array technology allows the simultaneous assessment of the expression of thousands of genes. This technology provides the possibility to identify new genes with pathologic impor tance in lymphomas, the identification of patterns of gene expression with diagnostic and/or prognostic significance, and the identification of new therapeutic targets.

Recognition of patterns of gene expression is complicated and requires sophisticated mathematical techniques. Early successes using this technology in lymphoma include the iden tification of previously unrecognized subtypes of DLBCL whose gene expression patterns resemble either those of follicular or germinal cen ter B (GCB) cells or activated peripheral blood B cells (ABC). Patients whose lymphomas have a GCB-like pattern of gene expression have a considerably better prognosis than those whose lymphomas have a pattern resembling ABCs. This improved prognosis is independent of other known prognostic factors. These subcategories have been more specifically refined into five subcategories, using more advanced genetic sequencing techniques, that differ with respect to biology and driver genes, as well as prognosis, and may have important treatment implications in the future. Similar information is being generated in FL and MCL. The challenge remains to provide information from such techniques in a clinically useful time frame. APPROACH TO THE PATIENT Regardless of the type of lymphoid malignancy, the initial evalua tion of the patient should include performance of a careful history and physical examination. These will help confirm the diagnosis,

TABLE 113-4 Genetic Features of B- and T-Cell Lymphomas GENETIC FEATURE GENES LYMPHOMA t(8;14) t(2;8) t(8;22) MYC/IgH MYC/Igκ MYC/Ig λ Burkitt’s lymphoma t(11;14) BCL1 (CCND1)/IgH Mantle cell lymphoma; multiple myeloma t(14;18) t(3;14) BCL2/IgH BCL6/IgH Follicular lymphoma, diffuse large B-cell lymphoma (DLBCL) t(11;18) t(1;14) t(14;18) t(3;14) API2/MALT1 BCL10/IgH MALT1/IgH FOXP1/IgH MALT lymphoma Trisomy 3 7q21 deletion Unknown CDK6 Splenic marginal zone lymphoma t(9;14) 6q21 deletion PAX5/IgH Unknown Lymphoplasmacytic lymphoma inv(14) t(14;14) TCRα/TCL1 Peripheral T-cell lymphoma, NOS; T-PLL t(2;5) t(1;2) t(2;3) t(2;17) inv(2) NPM1/ALK TPM3/ALK TFG/ALK CTLC/ALK ATIC/ALK Anaplastic large-cell lymphoma (ALCL) Trisomy 3 Trisomy 5 Unknown Unknown Angioimmunoblastic T-cell lymphoma Isochromosome 7q Unknown Hepatosplenic T-cell lymphoma Abbreviations: MALT, mucosa-associated lymphoid tissue; NOS, not otherwise specified; T-PLL, T-cell prolymphocytic leukemia. identify those manifestations of the disease that might require prompt attention, and aid in the selection of further studies to optimally characterize the patient’s status to allow the best choice of therapy. It is difficult to overemphasize the importance of a care fully done history and physical examination. They might provide observations that lead to reconsidering the diagnosis, provide hints at etiology, clarify the stage, and allow the physician to establish rap port with the patient that will make it possible to develop and carry out a therapeutic plan. The duration of symptoms and pace of symptomatic progres sion are important in distinguishing aggressive from more indo lent lymphomas, as are the presence or absence of “B” symptoms, such as fevers, night sweats, or unexplained weight loss. Patients should be asked about localizing symptoms that may point toward lymphomatous involvement of specific sites, such as the chest, abdomen, or CNS. Comorbid diagnoses that may impact therapy or monitoring on therapy should be reviewed and acknowledged, including a history of diabetes or congestive heart failure. A physi cal examination should pay close attention to all the peripherally accessible sites of lymph nodes; the liver and spleen size; Waldeyer’s ring; whether there is a pleural or pericardial effusion or abdominal ascites; whether there is an abdominal, testicular, or breast mass; and whether there is cutaneous involvement because all of these findings may influence further evaluation and disease management. Laboratory studies should include a complete blood count, routine chemistries, liver function tests, and serum protein elec trophoresis to document the presence of circulating monoclonal paraproteins. The serum β2-microglobulin level and serum lactate dehydrogenase (LDH) are important independent prognostic fac tors in NHL. Staging of certain diseases may involve a bone mar row biopsy; results of other laboratory

and staging studies may also warrant a marrow evaluation. A lumbar puncture for evaluation of lymphomatous involvement may be indicated in the setting of concerning neurologic signs or symptoms or diseases that are high

risk for CNS involvement. The latter may include disease involv ing the paranasal sinuses, testes, breast, kidneys, adrenal glands, and epidural space, as well as highly aggressive histologies like BL. Since HIV and hepatitis B and C infection can be risk factors for developing NHL, and since treatment for some NHLs can result in the potentially life-threatening reactivation of hepatitis B, patients with a new diagnosis of NHL should be screened for these viruses as well. Lymphoma histology and clinical presentation dictate which imaging studies should be ordered. Chest, abdominal, and pelvic computed tomography (CT) scans are essential for accurate stag ing to assess lymphadenopathy for indolent lymphomas, whereas positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG-PET) is useful for aggressive lymphomas, including BL, DLBCL, plasmablastic lymphoma, and the aggressive T-cell NHLs. FDG-PET is highly sensitive for detecting both nodal and extra nodal sites involved by NHL. The intensity of FDG avidity, or standardized uptake value (SUV), correlates with histologic aggres siveness, and may be useful in cases when disease transformation of an indolent lymphoma to a diffuse aggressive lymphoma is sus pected. PET scanning can also differentiate between treated disease and active disease at the end of therapy in patients with residual masses on CT scans. Consensus recommendations regarding PET scanning were published as a result of an International Harmoniza tion Project and state that PET should only be used for DLBCL and HL, that scanning during therapy should only be done as part of clinical trials, and that the end-of-treatment scan should not be done before 3 weeks but preferably 6–8 weeks after chemotherapy and 8–12 weeks after radiation or chemoradiotherapy. There is no evidence that long-term follow-up should include PET scanning. More recently, though, PET scan results at the end of therapy for FL have been associated with prognosis, with patients with residual PET-avid disease at the end of treatment having a poorer prognosis than those who are PET negative, and so it may be used for this prognostic purpose. Finally, magnetic resonance imaging (MRI) is useful in detecting bone, bone marrow, and CNS disease in the brain and spinal cord. The staging evaluation is outlined in Table 113-5. The Ann Arbor staging system developed in 1971 for HL was adapted for staging NHLs (Table 113-6). This staging system focuses on the number of tumor sites (nodal and extranodal), location, and the presence or absence of systemic, or B, symptoms. Table 113-6 summarizes the essential features of the Ann Arbor system. This anatomic based system is less useful in NHL, which dis seminates widely, not in an ordered stepwise fashion. A majority of patients with NHL have advanced-stage disease at diagnosis. Apart TABLE 113-5 Staging Evaluation for Non-Hodgkin’s Lymphoma Physical examination Documentation of B symptoms Laboratory evaluation Complete blood counts Liver function tests Uric acid Calcium Serum protein electrophoresis Serum β2-microglobulin Chest radiograph CT scan of abdomen, pelvis, and usually chest Bone marrow biopsy Lumbar puncture in lymphoblastic, Burkitt’s, and diffuse large B-cell lymphoma with positive marrow biopsy Gallium scan (SPECT) or PET scan in large-cell lymphoma Abbreviations: CT, computed tomography; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

TABLE 113-6 Ann Arbor Staging for Lymphomaa STAGE DESCRIPTION I Involvement of a single lymph node region (I) or single extranodal site (IE) II Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous, extralymphatic organ or tissue (IIE) III Involvement of lymph node regions on

both sides of the diaphragm (III), which may include the spleen (IIIS), or limited, contiguous, extralymphatic organ or tissue (IIIE), or both (IIIES) IV Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement aAll stages are further subdivided according to the absence (A) or presence (B) of systemic B symptoms including fevers, night sweats, and/or weight loss (>10% of body weight over 6 months prior to diagnosis). from early-stage disease limited to a radiation field where local therapy with radiation is an option, all other disease is treated the same regardless of stage. Histology and clinical parameters at pre sentation are more important than stage with respect to prognosis. The International Prognostic Index (IPI) is perhaps the best predic tor of outcome (Table 113-7). The IPI was developed based on the analysis of >2000 patients with aggressive NHLs treated with an anthracycline-containing regimen. Age (≤60 vs >60), serum LDH (≤ normal vs > normal), performance status (0 or 1 vs 2–4), stage (I or II vs III or IV), and extranodal involvement (<1 site vs >1 site) were identified as independently prognostic for overall survival (OS). A point is awarded for each risk factor and then summed, defining four risk groups: low (0 or 1); low-intermediate (2); highintermediate (3); and high (4–5). The 5-year OS rates for patients with scores of 0–1, 2, 3, and 4–5 were 73, 51, 43, and 26%, respec tively. The age-adjusted IPI separates patients ≤60 from patients

> 60. For the age-adjusted IPI, only stage, LDH, and performance status were important. Younger patients with 0, 1, 2, or 3 risk factors had 5-year survival rates of 83, 69, 46, and 32%, compared to 56, 44, 37, and 21% for older patients. When factoring in the introduction and clinical benefit of rituximab, the 4-year progression-free sur vival rates are 94, 80, and 53% for 0–1, 2, or 3 or more risk factors, respectively. CHAPTER 113 Non-Hodgkin’s Lymphoma The Follicular Lymphoma International Prognostic Index (FLIPI) is a similar predictive model for FL, derived from the analysis of >4000 patients. Age >60, stage III/IV disease, the TABLE 113-7 International Prognostic Index for NHL Five Clinical Risk Factors Age ≥60 years Serum lactate dehydrogenase levels elevated Performance status ≥2 (ECOG) or ≤70 (Karnofsky) Ann Arbor stage III or IV 1 site of extranodal involvement For Diffuse Large B-Cell Lymphoma 0, 1 factor = low risk 35% of cases; 5-year survival, 73% 2 factors = low-intermediate risk 27% of cases; 5-year survival, 51% 3 factors = high-intermediate risk 22% of cases; 5-year survival, 43% 4, 5 factors = high risk 16% of cases; 5-year survival, 26% For Diffuse Large B-Cell Lymphoma Treated With R-CHOP 0 factor = good 10% of cases; 4-year survival, 94% 1, 2 factors = intermediate 45% of cases; 4-year survival, 80% 3, 4, 5 factors = poor 45% of cases; 4-year survival, 53% Abbreviations: ECOG, Eastern Cooperative Oncology Group; NHL, non-Hodgkin’s lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

presence of >4 nodal sites, an elevated serum LDH concentration, and a hemoglobin <12 were identified as independent prognostic variables, and summation of each variable identified three

risk groups. The median 10-year survival rates for patients with zero to one (low risk), two (intermediate risk), or three or more (high risk) of these adverse factors were 71, 51, and 36%, respectively. Similar disease-specific IPIs have been developed for MCL and periph eral T-cell lymphoma (PTCL) as well. These prognostic indices take into account the proliferative index and cell-surface markers, respectively. Finally, as mentioned previously, gene expression profiling has identified DLBCLs with differential prognoses: GCB and ABC, where GCB-like DLBCL is associated with a significantly better OS. A more readily accessible immunohistochemical algorithm has been developed, based on the presence or absence of CD10, BCL6, and MUM1, that correlates closely with gene expression profiles and can differentiate the majority of GCB from non–GCB-like DLBCL. These profiles have prognostic importance but, to date, do not alter treatment recommendations for the primary treatment of DLBCL. Current clinical trials do stratify by DLBCL subtype, and it appears that agents like the Bruton tyrosine kinase (BTK) inhibitor ibrutinib and lenalidomide are most active in non-GCB DLBCL in the relapsed setting. Treatment may then be differentiated by these subtypes in the future. PART 4 Oncology and Hematology CLINICAL FEATURES, TREATMENT, AND PROGNOSIS OF SPECIFIC NHL ■ ■MATURE B-CELL NEOPLASMS B-cell NHLs can be characterized into two broad groups—those that behave aggressively, require immediate or urgent treatment with combination chemotherapy regimens, and are potentially curable; and those that are more indolent in nature, can be observed and treated only when they cause symptoms or signs of organ function impair ment, are very responsive to therapy, but are not ultimately curable in the vast majority of cases. Among the aggressive diseases, the most common is DLBCL, and the most rapidly growing is BL. FL is the sec ond most common NHL and the most common indolent NHL. Other indolent NHLs include MZL, lymphoplasmacytic lymphoma (LPL), and hairy cell leukemia (HCL). MCL is an intermediate-grade lym phoma that shares some characteristics with the aggressive lymphomas (fairly urgent need for treatment and aggressive upfront combination chemotherapy regimens), but like the indolent lymphomas, it is not readily curable with conventional-dose therapies. Burkitt’s Lymphoma Burkitt’s lymphoma/leukemia (BL) is a rare disease in adults in the United States, making up <1% of NHL, but it makes up ~30% of childhood NHL. It is one of the fastest growing neo plasms, with a doubling time of <24 h. In general, it is a pediatric tumor that has three major clinical presentations. The endemic (African) form presents as a jaw or facial bone tumor that spreads to extranodal sites including ovary, testis, kidney, breast, and especially the bone marrow and meninges. The nonendemic form has an abdominal presentation with massive disease, ascites, and renal, testis, and/or ovarian involve ment and, like the endemic form, also spreads to the bone marrow and CNS. Immunodeficiency-related cases more often involve lymph nodes and may present as acute leukemia. BL has a male predominance and is typically seen in patients <35 years of age. On biopsy, there is a monotonous infiltration of medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm with vacuoles. The proliferation rate is ~100%, and tingible body macro phages give rise to the classic “starry sky” appearance of this tumor (Fig. 113-4). Tumor cells are positive for B-cell antigens CD19 and CD20 and surface immunoglobulin. They are also uniformly positive for CD10 and BCL6 but negative for BCL2. Endemic BLs are EBV posi tive, whereas the majority of nonendemic BLs are EBV negative. BL is associated with a translocation involving MYC on chromosome 8q24 in >95% of the cases. The most common partners are chromosomes 14,

FIGURE 113-4 Burkitt’s lymphoma. The neoplastic cells are homogeneous, mediumsized B cells with frequent mitotic figures, a morphologic correlate of high growth fraction. Reactive macrophages are scattered through the tumor, and their pale cytoplasm in a background of blue-

staining tumor cells gives the tumor a so-called starry sky appearance. 2, or 22, rearrangements that produce fusions of MYC with either the IgH (80%), kappa (15%), or lambda (5%) light chain genes, respectively. While exquisitely chemosensitive, it is imperative that treatment for BL be initiated quickly given the rapid doubling time and high morbidity of this disease. There are several effective intensive combi nation chemotherapy regimens, all of which incorporate high doses of cyclophosphamide. Prophylactic therapy to the CNS is mandatory. Cure can be expected in 80–90% of patients when treated promptly and correctly. Modified Magrath and dose-adjusted EPOCH-R (ritux imab, infusional etoposide/vincristine/doxorubicin, cyclophospha mide, prednisone) are highly effective regimens. Salvage therapy has been generally ineffective in patients whose disease progresses after upfront therapy, emphasizing the importance of the initial treatment approach and referral to a tertiary cancer center with experience treat ing this disease. Diffuse Large B-Cell Lymphoma DLBCL is the most common histologic subtype of NHL diagnosed, representing about one-third of all cases. Previously felt to be “one disease,” it is now recognized as a heterogeneous collection of multiple entities. It is slightly more com mon in Caucasians and men, and the median age at diagnosis is 64. The relative risk (RR) of DLBCL is higher among people with affected first-degree relatives (RR 3.5-fold), and patients with congenital or acquired immunodeficiency, patients on immunosuppression, and patients with autoimmune disorders also have a higher risk of develop ing DLBCL, often EBV-related. The majority of patients present with advanced-stage disease, with only 30–40% of patients having stage I or II disease; ~40% of patients will have “B” symptoms, and 50% of patients will have an elevated LDH. Up to 40% of patients will have involvement of non–lymph node sites including bone marrow, CNS, gastrointestinal tract, thyroid, liver, and skin. Patients with extensive bone marrow involvement or involvement of the testes, breast, kidney, adrenal gland, paranasal sinus, or epidural space are at increased risk of CNS dissemination. The tumor consists of a diffuse proliferation of large, atypical lym phocytes with a high proliferative index (Fig. 113-5). These cells typi cally express the B-cell antigens CD19, CD20, and CD79a. Expression of CD10 and BCL6 is consistent with the tumor cell being of germinal center origin (GCB), while the expression of MUM1 corresponds with the non–germinal center or ABC subtype. BCL2 is overexpressed in anywhere from 25 to 80% of DLBCLs, whereas BCL6 is positive in more than two-thirds of cases, as the result of translocations, gain of copy number, or promoter mutations. MYC is rearranged in 10% of DLBCLs, and ~20% of MYC-rearranged cases have a concurrent BCL2 rearrangement, a combination referred to as “double-hit lymphoma.” These double-hit lymphomas constitute one subtype of high-grade B-cell lymphoma (HGBL) and are associated with an extremely poor

FIGURE 113-5 Diffuse large B-cell lymphoma. The neoplastic cells are heterogeneous but predominantly large cells with vesicular chromatin and prominent nucleoli. prognosis with a median OS of only 12–18 months. The other subtype of HGBL is called HGBL not otherwise specified (NOS) and is defined based on blastoid or Burkitt-like morphologic features. Amplification and/or overexpression of MYC independent of rearrangements or amplification have also been described and are also associated with a poor, albeit better, prognosis. Combination chemotherapy offers potentially curative therapy for DLBCL, regardless of the stage. The addition of the anti-CD20 antibody rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) improved survival beyond CHOP alone and has been the standard first-line chemotherapy for this disease for decades. The combination of R-CHP (R-CHOP without vincristine) and the antibody-drug conjugate (ADC) polatuzumab was compared to R-CHOP in the randomized POLARIX study and demonstrated a progression-free survival benefit with polatuzumab–R-CHP, leading to the approval

of this regimen as a new standard option for patients with IPI 2 or higher disease. For patients with early-stage disease localized to a radiation field, treatment options include full-course chemotherapy with R-CHOP every 3 weeks for six cycles or abbreviated chemo therapy for three to four cycles followed by involved field radiotherapy. The randomized FLYER studies compared four versus six cycles of R-CHOP chemotherapy for early favorable-risk DLBCL and showed no benefit to a more extended course of chemotherapy. For advancedstage DLBCL, therapy is with a full course of chemotherapy. On aver age, ~65–70% of patients with DLBCL can be expected to be cured with this approach, and the likelihood of cure is predicted by the IPI, gene expression profile cell of origin, and/or MYC cytogenetics and expres sion. Several studies, other than the above mentioned POLARIX study, have investigated alternative anthracycline-containing chemotherapy regimens and/or consolidation autologous stem cell transplanta tion in first remission for higher-risk disease without improvement over R-CHOP alone. Dose-adjusted R-EPOCH is one such regimen. Although this regimen did not appear to be better than R-CHOP for DLBCL in one multicenter clinical trial, it is often used to treat primary mediastinal large B-cell lymphoma and double-hit DLBCL based on results from phase 2 and retrospective studies, respectively. CNS pro phylaxis with either intrathecal chemotherapy or high-dose systemic methotrexate and leucovorin rescue offers unclear benefit to patients at high risk for CNS relapse and is increasingly not being used based on results of retrospective and observational studies. Over one-third of patients will either have primary refractory disease or disease that relapses after first-line chemotherapy. These patients may still be cured with either salvage chemotherapy regimens followed by autologous stem cell transplantation (for patients relaps ing >12 months from the completion of therapy) or CD19 chimeric antigen receptor (CAR) T cells (for patients with primary refractory or early relapsing disease or those who are not felt to be autologous stem cell transplantation candidates). However, patients with a poor

performance status or certain comorbid conditions who are not can didates for such approaches are often managed with palliative inten tions. Radiation to symptomatic areas of disease can be transiently helpful. Less intensive chemotherapy with drugs such as gemcitabine, cytarabine, or bendamustine can help control disease and symptoms for a limited period of time. Newer drugs including the CD79b ADC polatuzumab in combination with bendamustine and rituximab (BR), the high-affinity CD19 monoclonal antibody (mAb) tafasitamab in combination with lenalidomide, the CD19 ADC loncastuximab, and the CD20-CD3 bispecific antibodies epcoritamab and glofitamab have been approved for use in these palliative settings as well as for patients who relapse after CAR-T therapy or autologous stem cell transplanta tion. Some of these agents can be used as a bridge to a definitive allo geneic stem cell transplantation

For patients in whom more aggressive therapy is an option, treatment for late relapsing patients is with combination chemotherapy using vari ous combinations of drugs primarily in order to identify patients with chemosensitive disease. Patients with chemosensitive disease have the greatest likelihood of benefiting from high-dose chemotherapy and autologous stem cell transplant, which improves response duration and survival over salvage chemotherapy alone and leads to long-term disease-free survival in ~40–50% of patients. The randomized ZUMA-7 and TRANSFORM studies of the CD19 CAR-T therapies axicabtagene ciloleucel (axi-cel) and lisocabtagene autoleucel (liso-cel) established both of these CAR-T therapies as the most effective option for patients with primary refractory or early (<12 months) relapsing disease over salvage chemotherapy and autologous stem cell transplantation. CHAPTER 113 For this therapy, T cells are collected from a patient and

are then genetically modified to express a receptor that will bind to a surface antigen expressed on the patient's own tumor cells. In the case of B-cell malignancies, CD19 has been targeted most commonly. After infu sion, autologous CAR-T cells home to sites of disease and persist over time. The CARs consist of an extracellular antigen recognition domain (typically a single-chain Fv variable fragment from a monoclonal anti body) linked via a transmembrane domain to an intracellular signaling domain (usually the CD3ζ endodomain), resulting in the redirection of T-cell specificity toward target antigen-positive cells, and one or more costimulatory domains including CD28, 4-1BB, or OX40 to enhance cytokine secretion and effector cell expansion and prevent activationinduced apoptosis and immune suppression by tumor-related metabo lites. For late relapsing patients with chemorefractory disease, CAR-T therapies such as axi-cel, liso-cel, and tisagenlecleucel (tisa-cel) offer a potentially curative option in the third-line setting as well. In this set ting, the response rate of CAR-T cells is >80%, with >50% of patients achieving a complete response. These responses appear to be durable, with 40% of patients in remission at long-term follow-up. Non-Hodgkin's Lymphoma Other large B-cell lymphomas include intravascular large B-cell lymphoma, T-cell/histiocyte–rich large B-cell lymphoma, EBV-positive DLBCL of the elderly, and ALK-positive large B-cell lymphoma. Patients with the latter two diseases tend to have a poor progno sis, whereas the addition of rituximab to CHOP chemotherapy has dramatically improved outcomes with intravascular large B-cell lymphoma, and the outcomes in T-cell/histiocyte–rich large B-cell lymphoma are similar to DLBCL. R-CHOP remains the treatment of choice for each of these lymphomas. Follicular Lymphoma FLs are the second leading NHL diagnosis in the United States and Europe and make up 22% of NHLs worldwide and at least 30% of NHLs diagnosed in the United States. This type of lymphoma can be diagnosed accurately on morphologic findings alone and has been the diagnosis in the majority of patients in therapeutic trials for "low-grade" lymphoma in the past. Evaluation of an adequate biopsy by an expert hematopathologist is sufficient to make a diagnosis of FL. The tumor is composed of small cleaved and large cells in varying proportions organized in a follicular pattern of growth (Fig. 113-6). Confirmation of B-cell immunopheno type (monoclonal immunoglobulin light chain, CD19, CD20, CD10, and BCL6 positive, and CD5 and CD23 negative) and the existence of t(14;18) and abnormal expression of BCL2 protein are confirmatory.

FIGURE 113-6 Follicular lymphoma. The normal nodal architecture is effaced by nodular expansions of tumor cells. Nodules vary in size and contain predominantly small lymphocytes with cleaved nuclei along with variable numbers of larger cells with vesicular chromatin and prominent nucleoli. While >85% of FLs will harbor a t(14;18) and overexpress the anti apoptotic protein BCL2, this genetic event is necessary but not suffi cient for malignant transformation of the B lymphocytes, and multiple genetic events are required for the development of FL. Studies have identified the most common recurrent genetic events in FL, and they included mutations in several epigenetic modifying genes, including MLL2, EZH2, CREBBP, and EP300. The major differential diagnosis is between lymphoma and reactive follicular hyperplasia. The coexistence of DLBCL must be considered. Patients with FL are often subclassi fied, or graded, into those with predominantly small cells, those with a mixture of small and large cells, and those with predominantly large cells. The WHO classification adopted grading from I to III based on the number of centroblasts, or large cells, counted per high-power field (hpf): grade I, from 0 to 5 centroblasts/hpf; grade II, from 6 to 15 centroblasts/hpf; and grade III, >15 centroblasts/hpf. Grade III has been subdivided into grade IIIa, in which centrocytes predominate, and follicular large B-cell lymphoma (FLBCL), in which there are sheets of centroblasts. While this distinction cannot be made simply or very reproducibly, these subdivisions do have prognostic significance. Patients with FL with predominantly large cells have a

higher prolifera tive fraction, progress more rapidly, and have a shorter OS with simple chemotherapy regimens. FLBCL is an aggressive disease and consid ered most similar to DLBCL and treated as such with curative intent. PART 4 Oncology and Hematology The most common presentation for FL is with new, painless lymph adenopathy. Multiple sites of lymphoid involvement are typical, and unusual sites such as epitrochlear nodes are sometimes seen. However, essentially any organ can be involved, and extranodal presentations do occur. Most patients do not have an elevated LDH or fevers, night sweats, or weight loss, although histologic transformation to DLBCL does occur at a rate of ~3% per year and can be associated with these signs or symptoms. As discussed previously, prognosis is best predicted by the FLIPI. Staging is typically done with CT scans of the chest, abdomen, and pelvis, as well as the neck if neck disease is suspected, although PET/CT scans can be helpful in cases where disease trans formation is suspected, as transformed disease will be more FDG avid than indolent disease, or for confirmation of early-stage disease, where definitive local therapy with radiation may be considered. Although FL is highly sensitive to chemotherapy and radiotherapy, these therapies are usually not ultimately curative, except in the setting of early-stage disease. If the disease can be encompassed in a radiation field, involved field radiotherapy at a dose of 24–30 Gy may be cura tive, with 5-, 10-, and 15-year freedom from treatment failure rates of 72, 46, and 39%, and overall 5-, 10-, and 15-year survival rates of 93, 75, and 62%, respectively. If radiation therapy would not be toler ated or if a patient prefers not to receive radiation, observation is a reasonable alternative with a median time to treatment not reached at

7 years of follow-up in one study. Many of these patients are diagnosed

incidentally or at a time when their lymphoma is not causing symp toms or signs of organ function impairment. Numerous studies have shown that treating patients with asymptomatic disease does not improve survival compared with a program of close observation, with treatment reserved for symptomatic disease progression or organ dys function. Thus, asymptomatic patients should be observed. When systemic treatment is indicated, a variety of treatment options are available, including the use of the monoclonal antibody against CD20, rituximab, alone or in combination with chemotherapy or with the oral drug lenalidomide. Treatment decisions are often determined by the indication for treatment and/or by the volume of disease being treated. For patients requiring therapy for inflamma tory or autoimmune phenomenon thought to be driven by FL or for patients with low-volume disease, single-agent rituximab is associ ated with a response rate of ~70% and a median response duration of

> 2 years. This response duration is improved with the addition of main tenance rituximab following a favorable response to rituximab induc tion therapy. For patients with a larger volume of disease at the time of treatment initiation, the addition of rituximab (R) to chemotherapy regimens such as CHOP or cyclophosphamide, vincristine, and pred nisone (CVP) has improved survival in this disease. The combination of bendamustine and rituximab (BR) has been compared to R-CHOP and results in longer response duration and less toxicity. Thus, BR has become the standard of care for the first-line therapy of medium- to high-volume FL. Similarly, the addition of maintenance rituximab following a

> good response to R-CHOP or R-CVP improves response duration when used in newly treated FL patients. A newer anti-CD20 antibody, obinutuzumab, has been tested in combination with chemo therapy in a randomized trial against rituximab plus chemotherapy in previously untreated FL. The obinutuzumab combinations resulted in improvements in minimal residual disease (MRD) negativity as well as progression-free survival at the expense of more infection and infusion reactions. Based on these results, both rituximab plus chemotherapy and obinutuzumab plus chemotherapy are options for untreated FL in need of treatment. The superiority of one over the other has not been established. Finally, a randomized study has compared rituximab plus chemotherapy with either BR, R-CHOP, or R-CVP to rituximab plus lenalidomide, and results were similar in both arms, thus making the chemotherapy-free rituximab-lenalidomide regimen an option for the frontline treatment of FL. In patients with FL, the disease nearly always recurs following therapy, after which retreatment is again reserved for symptomatic disease or disease interfering with organ function. Single-agent ritux imab or alternative chemotherapy regimens, with both rituximab and obinutuzumab, can again be employed. Both autologous and allogeneic hematopoietic stem cell transplantations yield high complete response rates in patients with relapsed FL, and long-term remissions can occur in 40 and 60% of patients, respectively. The latter is associated with con siderable treatment-related morbidity and mortality and so is usually reserved for patients with multiply relapsed FL that is no longer respon sive to chemotherapy. More targeted oral therapies like lenalidomide and the EZH2 inhibitor tazemetostat are active in relapsed FL. The PI3 kinase inhibitors idelalisib, duvelisib, and copanlisib are active in FL but are no longer available given the lack of randomized confirmatory evidence to support their efficacy. The anti-CD19–directed CAR-T therapies axi-cel and tisa-cel have been approved for relapsed FL in the third-line setting and beyond, with complete responses seen in >80% of patients with multiply relapsed disease, and with many of those responses proving durable, albeit with limited follow-up. Longer followup is needed to determine if this may be a definitive treatment strategy for a subset of relapsed FL patients. The CD20-CD3 bispecific antibody mosunetuzumab has been approved for FL in the third-line setting and beyond as well and offers a highly effective and potentially less toxic option for patients compared with CAR-T therapy. On average, most patients will live with FL for 15–20 years, a number that is increasing given our improved understanding of the genetics and microenviron ment of FL and the increasing number of drugs and therapies being tested in this disease. However, in addition to a high-risk FLIPI, patients who do not have a complete metabolic response by PET/CT scanning

to their primary therapy and patients who relapse within 2 years of the completion of their primary chemotherapy tend to do poorly with chemotherapy and should be considered for some of these non chemotherapy options. Randomized trials comparing chemotherapy,

lenalidomide-based therapy, and CAR-T therapy in the second-line set ting for these refractory or early relapsing patients are underway. Patients with FL have a high rate of histologic transformation to DLBCL (~3% per year). This is recognized ~40% of the time during the course of the illness by repeat biopsy and is present in almost all patients at autopsy. This transformation is usually heralded by rapid growth of lymph nodes—often localized—and the development of systemic symptoms such as fevers, sweats, and weight loss. When this happens in patients who have had previously untreated FL, treatment with R-CHOP chemotherapy, as for DLBCL, can be curative for the aggressive component while the FL may eventually recur. In patients with previously treated FL that transforms to DLBCL, prognosis is poor, and successful therapy with an aggressive combination chemo therapy regimen should be consolidated with an autologous stem cell transplant. CAR-T therapy and other therapies for relapsed/refractory DLBCL are options for chemorefractory transformations. Finally, as discussed previously, grade IIIb FL is more similar to DLBCL than it is to FL and should be treated as such. Marginal Zone Lymphoma The second most common indolent B-cell NHL is MZL. There are three main types: splenic MZL, extrano dal MZL of MALT, and nodal MZL. Nodal MZL most closely resembles FL clinically, and much of the way we manage and treat it is based on studies done in FL. Tumor biopsies in this disease show parafollicular and perivascular infiltration by monocytoid-appearing atypical lymphocytes with folded nuclear contours that are positive for CD19, CD20, and CD79a but negative for CD10 and largely negative for CD5. Some cases can have plasmacytoid differentiation and can be associated with a monoclonal expression of kappa or lambda light chains and with small monoclonal immunoglob ulin spikes. Treatment is often similar to that of FL, with the exception that the BTK inhibitors ibrutinib and zanubrutinib are highly active in this disease, while largely disappointing in FL, and are good treatment options for relapsed nodal MZL as well as other MZL subtypes. CAR-T therapy is not approved in MZL but has been tested in clinical trials with similar efficacy to what has been shown in FL. Splenic MZL is largely a disease of older Caucasian patients; infec tion with hepatitis C is a risk factor for this disease, and treatment of hepatitis C can result in regression of the lymphoma. Patients present with a lymphocytosis with or without cytopenias and splenomegaly. Bone marrow involvement is common. Diagnosis can be made by flow cytometry of the peripheral blood; malignant lymphocytes will be positive for surface immunoglobulin, CD19, and CD20 and will generally lack CD5 and CD10. On peripheral smear, they have small nuclei and abundant cytoplasm with “shaggy” or villous projections. It can be differentiated from HCL by the absence of CD25, CD103, and annexin A1. Recurrent cytogenetic abnormalities include trisomy 3 and abnormalities of chromosome 7q. Therapy is indicated for symp tomatic disease or significant cytopenias. Splenectomy is reasonable for selected patients with excellent relief of symptoms and cytopenias. Splenectomy is associated with an overall response rate of 85% and estimated progression-free survival and OS rates at 5 years of 58 and 77%, respectively. Single-agent rituximab can improve splenomegaly and cytopenias in >90% of patients. In a study of induction with weekly rituximab followed by maintenance, the response rate was 95%, with OS and progression-free survival rates at 5 years of 92 and 73%, respectively. Other options for therapy at relapse are similar to those used for FL and include retreatment with rituximab, alkylating agents, and purine analogues in combination with rituximab. The survival rate of patients is in excess of 70% at 10 years. MALT lymphoma is an MZL lymphoma of extranodal tissue, most commonly the stomach, but other common sites include the skin, sali vary glands, lung, small bowel, ocular adnexa, breasts, bladder, thyroid, dura, and synovium. It is associated with states of chronic inflamma tion due to either autoimmune diseases like Sjögren’s syndrome or

Hashimoto’s thyroiditis or chronic infections with organisms such as H. pylori (gastric), Borrelia burgdorferi (skin), C. psittaci (conjunctiva), C. jejuni (intestines), and hepatitis C virus. The essential pathologic feature of MALT lymphoma is the presence of lymphoepithelial lesions, which result from invasion of mucosal glands and crypts by the neo plastic lymphocytes. These cells are positive for CD19, CD20, and CD79a and negative for CD5 and CD10. Recurrent cytogenetic abnormalities include t(11;18), t(14;18), t(1;14), t(3;14), and trisomy 8. The t(11;18) is most common, occurring in up to 50% of MALT lymphomas. It results in the fusion of the apoptosis inhibitor 2 (API2) gene and the MALT1 gene, resulting in activation of nuclear factor-κB (NF-κB). Unlike other indolent B-cell lymphomas, MALT lymphomas present most commonly with stage I or II disease. In these cases, radiation therapy may be curative. Alternatively, patients may respond to antibiotics for the associated underlying infection. Treatment of symptomatic or organ-impairing relapsed, refractory, or advanced-stage disease is similar to approaches used in FL with chemotherapy, immunotherapy, or chemoimmunotherapy.

Lymphoplasmacytic Lymphoma About 1% of all NHLs will be LPLs, which are indolent B-cell NHLs with lymphoplasmacytic differentiation, most commonly associated with a monoclonal IgM paraprotein. Nearly all patients will have stage IV disease at diagnosis with bone marrow involvement. Patients with high levels of circulating IgM paraproteins constitute a specific entity known as Waldenström’s macroglobulinemia and can have symptoms due to hyperviscosity as a result of the circulating IgM. Activating mutations in MYD88, an adap tor protein that is involved in signaling downstream of the Ig receptor leading to NF-κB activation, are present in >90% of cases. Tumor biop sies are notable for proliferation of small lymphocytes, lymphoplasma cytic cells, and plasma cells, and malignant lymphocytes are positive for CD19, CD20, and surface IgM but generally negative for CD5 and CD10. Like the other indolent NHLs, treatment is indicated for disease that causes symptoms or interferes with organ function; hyperviscosity related to elevated serum IgM and paraneoplastic neuropathy are addi tional indications for therapy. Single-agent rituximab may be useful for low-volume disease but can be associated with a transient rise in serum IgM concentrations that can cause or exacerbate hyperviscos ity. Chemoimmunotherapy with regimens such as BR and rituximab, cyclophosphamide, and dexamethasone is active, as are myeloma therapies such as bortezomib. Ibrutinib and zanubrutinib in combina tion with rituximab are highly active in this disease and are options for both previously untreated and relapsed disease. Given that 85% of IgM remains intravascular, acute relief of hyperviscosity symptoms can be obtained by plasmapheresis. For recurrent disease, one can often use agents that were previously used. For patients with more refractory LPL, the mammalian target of rapamycin (mTOR) inhibitor everolimus and the bcl-2 inhibitor venetoclax are active. Selected patients with relapsed disease are considered for high-dose therapy with autologous or allogeneic stem cell transplantation. The results seen are similar to those of other indolent lymphomas. CHAPTER 113 Non-Hodgkin’s Lymphoma Mantle Cell Lymphoma MCL composes ~6% of NHLs. It is an intermediate-grade lymphoma that, like the indolent B-cell NHLs, is not curable with conventional therapies but, like the aggressive lymphomas, often requires more aggressive chemoimmunotherapy regimens with or without an autologous stem cell transplant to achieve a reasonable response duration. This therapy is not curative, however, and median survival with this disease is on the order of 5–10 years. An exception to this is a more indolent SOX11 variant that often presents with circulating disease with splenomegaly but without significant lymphadenopathy and with a low Ki67 (<10%). This subset behaves more like the indolent B-cell NHLs and can be observed until treat ment is indicated by symptoms or organ function impairment. Simi larly, there

is a blastic variant with a high Ki67 index that is associated with a poor prognosis and a median OS of only 18 months. For other patients, prognosis is best predicted by the biologic MCL International Prognostic Index (MIPI), which factors in age, performance status, LDH, white blood cell count, and Ki67 expression to determine a risk

group. This disease is more common in men, and the average age of diagnosis is 63. MCLs with a mutation in TP53 or a complex karyo type are particularly high risk as well. Over two-thirds of patients will have stage IV disease, mostly with bone marrow and peripheral blood involvement, at the time of diagnosis. Another common extranodal site of involvement is the gastrointestinal tract, where diffuse lymphoma tous polyposis may be seen.

The pathognomonic cytogenetic finding in MCL is t(11;14), which brings the gene for the cell cycle control protein cyclin D1 under the control of the immunoglobulin heavy chain gene promoter on chromo some 14. This translocation is present in >90% of cases. The remaining cases usually overexpress cyclin D2, cyclin D3, or cyclin E. Tumor cells also are positive for B-cell markers CD19 and CD20, as well as CD5. They usually lack CD10 and CD23. Therapies for MCL are evolving. Patients with localized dis ease might be treated with combination chemotherapy followed by radiotherapy; however, these patients are exceedingly rare. Similarly, patients with the indolent variant can be observed until disease pro gresses to cause symptoms or signs of organ function impairment. For the usual presentation with disseminated disease, standard lymphoma treatments like R-CHOP have been unsatisfactory, with the minority of patients achieving complete remission. The addition of high-dose cytarabine to an R-CHOP–like backbone with or without consolidation autologous stem cell transplantation in first remission has improved progression-free survival, but it has not elicited cures in this disease. These include the Nordic regimens and R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytara bine, and methotrexate). BR has activity in this disease and is more effective and better tolerated than R-CHOP. Newer studies with short follow-up suggest that strategies that combine BR with cytarabine with or without autologous stem cell transplant may be effective and well tolerated. The SHINE study randomized patients to BR alone versus BR plus ibrutinib and showed a modest benefit with the addi tion of ibrutinib. It is not clear, however, if this benefit is greater than the sequencing of upfront BR followed by BTK inhibition at relapse. Maintenance rituximab, following a good response to induction che motherapy or after autologous stem cell transplant, also improves out comes over observation alone. Increasing evidence suggests that with modern induction therapies, high-dose chemotherapy and autologous stem cell rescue may no longer provide benefit in the frontline setting. The randomized European TRIANGLE study showed no benefit of autologous transplant when added to induction chemoimmunotherapy with ibrutinib followed by rituximab and ibrutinib maintenance. An ongoing randomized study in the United States is asking a similar question for patients who are treated with chemoimmunotherapy without upfront BTK inhibition. For relapsed disease, the BTK inhibi tors ibrutinib, acalabrutinib, and zanubrutinib have single-agent activ ity with a response rate of almost 70% but a response duration of only 18–24 months. These drugs are being explored in combination with chemotherapy as well as with the BCL2 antagonist venetoclax. AntiCD19–directed CAR-T therapies are approved for the treatment of relapsed/refractory MCL; two-thirds of patients who had progressed after chemoimmunotherapy (with or without an autologous stem cell transplant) and BTK inhibition have achieved complete responses, many of which are durable through limited follow-up. As in FL, longer follow-up is needed to determine if some of these patients may be cured, which would make this the only curative therapy for this

disease outside of an allogeneic stem cell transplantation. The noncovalent BTK inhibitor pirtobrutinib has activity in MCL that has progressed on prior covalent BTK inhibitors and is now approved in this setting. Drugs such as lenalidomide, venetoclax, bortezomib, and temsirolimus can similarly induce transient partial responses. Appropriate patients who respond to salvage therapy, with the exception of CAR-T therapy, should be considered for allogeneic stem cell transplant, which can lead to long-term disease-free survival in 30–50% of patients. PART 4 Oncology and Hematology ■ ■MATURE (PERIPHERAL) T-CELL DISORDERS Mature T-cell disorders include cutaneous lymphomas, such as mycosis fungoides, and the PTCLs, some of which are distinguished based on

specific clinical presentations or contexts or by molecular or biologic features, but many of which fall into the category of PTCL not other wise specified (NOS). T-cell NHLs are significantly rarer than B-cell NHLs, and as such, our understanding of their biology is less advanced and our therapies are less well developed. While some T-cell lympho mas, like mycosis fungoides, can behave indolently and some, like ALK-positive ALCL, can be cured with chemotherapy, the majority are associated with a poor prognosis. The advent of genomic technologies is enhancing our ability to understand the genetic and biologic basis of these neoplasms. Mycosis Fungoides Mycosis fungoides is also known as cutaneous T-cell lymphoma. This lymphoma is more often seen by dermatologists than internists. The median age of onset is in the mid-fifties, and the disease is more common in males and in blacks. Mycosis fungoides is an indolent lymphoma, with patients often having several years of eczematous or dermatitic skin lesions before the diagnosis is finally established. The skin lesions progress from patch stage to plaque stage to cutaneous tumors. Early in the disease, biopsies are often difficult to interpret, and the diagnosis may only become apparent by observing the patient over time. Adenopathy may reflect involvement with mycosis fungoides or be read as dermatopathic change. In advanced stages, the lymphoma can spread to lymph nodes and visceral organs. Patients with this lymphoma may develop general ized erythroderma and circulating tumor cells, called Sézary’s syndrome. Rare patients with localized early-stage mycosis fungoides can be cured with radiotherapy, often total-skin electron beam irradiation. More advanced disease has been treated with topical glucocorticoids, topical nitrogen mustard, phototherapy, psoralen with ultraviolet A (PUVA), extracorporeal photopheresis, retinoids (bexarotene), electron beam radiation, interferon, antibodies, fusion toxins, histone deacety lase inhibitors, brentuximab (for CD30+ disease), and systemic cyto toxic therapy. Mogamulizumab, an anti-CCR4 antibody, has activity in this disease and has been approved by the U.S. Food and Drug Adminis tration for this indication. Unfortunately, these treatments are palliative. Peripheral T-Cell Lymphoma, Not Otherwise Specified

PTCLs include a number of entities, which constitute 15% of all NHLs in adults. PTCL NOS, which composes 6% of all NHLs, is the term used for cases that are not other entities defined in the WHO classification. Named varieties include ALCL, angioimmunoblastic T-cell lymphoma (AITL), hepatosplenic T-cell lymphoma, enteropathy-associated T-cell lymphoma, and subcutaneous panniculitis T-cell lymphoma. PTCL NOS is a disease of older individuals, with a median age at presentation of 65, and the majority of patients will have advanced-stage disease at diagnosis, with involvement of the bone marrow, liver, spleen, and skin being common. Associated “B” symptoms and pruritis are also com mon. These lymphomas can be associated with a reactive eosinophilia as well as hemophagocytic syndrome. The IPI has been applied to PTCL NOS and provides some assessment of outcomes, but even the low-risk group has a median OS of just >2 years. This

diagnostic category is a collection of heterogeneous lympho mas that vary widely and lack typical findings of other specific PTCL subgroups. Because of this heterogeneity, histology, immunophe notype, and genetics are variable. Often lymph nodes are effaced by atypical lymphoid cells of various sizes, sometimes associated with vascular proliferation or an infiltrate of eosinophils and/or macro phages. As most of these lymphomas behave aggressively, note is often made of mitotic and apoptotic figures as well as geographic necrosis. The cells often are positive for CD3, and the majority of PTCL NOS is positive for CD4 rather than CD8, but some are negative for both markers. There can be loss of more mature T-cell markers like CD5 and CD7, and this is associated with a more aggressive course. There are some recurrent translocations, including t(7;14), t(11;14), inv(14), and t(14;14), all of which involve the TCR genes. The most common primary therapy for PTCL NOS involves a CHOP-like chemotherapy backbone—either CHOP alone or CHOP in combination with etoposide (CHOEP). The latter may provide the most benefit to younger patients and patients with more favorable dis ease risk factors. Brentuximab in combination with cyclophosphamide,

doxorubicin, and prednisone (CHP) has been tested in a randomized clinical trial against CHOP in CD30+ T-cell lymphomas; progressionfree survival was improved with the brentuximab-containing arm, and this was most pronounced for patients with ALCL (see below). Autolo gous stem cell transplant has been investigated for patients in their first remission and does seem to improve progression-free survival in certain contexts. Drugs such as gemcitabine, bendamustine, and prala trexate have activity in relapsed disease, as do the histone deacetylase inhibitors romidepsin and belinostat. The PI3 kinase inhibitor duvelisib is being investigated in these diseases with early signals of activity. All of these agents are associated with transient responses in a minority of patients. Patients should be considered for clinical trials. For patients who do achieve remission, reduced-intensity allogeneic stem cell trans plantation can yield long-term nonrelapse survival rates of ~40–50%. Angioimmunoblastic T-Cell Lymphoma AITL constitutes ~20% of T-cell NHLs and ~4% of all NHLs diagnosed. Patients present with a variety of signs and symptoms, most often including lymphade nopathy, hepatosplenomegaly, “B” symptoms, rash, polyarthritis, and hemolytic anemia. Over 80% of patients have advanced-stage disease at diagnosis, and bone marrow involvement is common. Polyclonal hypergammaglobulinemia is common, as are elevated LDH, eosino philia, a positive Coombs test, and opportunistic infections. On biopsy, lymph nodes are effaced by a polymorphous infiltrate of lymphocytes, ranging in size and shape, and of immunoblasts. The neoplastic lymphocytes are positive for CD3 as well as CXCL13, PD-1, CD10, and BCL6, most closely resembling CD4-positive follicular helper T cells. There is an expanded follicular dendritic cell network surrounding tumor cells. Scattered immunoblasts are often EBV posi tive and may give rise to secondary EBV-positive B-cell lymphomas at a later time. Genetic analysis of this disease has revealed recurrent mutations in TET2 (76%), DNMT3 (33%), and IDH2 (20%). A subset of AITL can remit with immunosuppression with agents like glucocorticoids or methotrexate. Most patients, however, will need combination chemotherapy with regimens like those used in PTCL NOS. Median response duration is short, and median OS is only 15–36 months. Treatment of relapsed disease is similar to that of relapsed PTCL NOS. Anaplastic Large-Cell Lymphoma ALCL is the next most com mon T-cell lymphoma after AITL but is more common in children, accounting for up to 10% of pediatric lymphomas. Approximately 40–60% of cases harbor t(2;5), which fuses a portion of the nucleolar protein nucleophosmin-1 (NPMI) gene to a part of the anaplastic lymphoma kinase (ALK) gene, the product of which has constitutive tyrosine kinase activity. These patients have a much more favorable prognosis compared to ALK-negative ALCL,

akin to that of DLBCL. There is an additional, more indolent and favorable subtype that occurs in the breast tissue of patients with breast implants, and there is a cuta neous variant. In general, this is a disease that is more common in men. ALK-positive disease is a disease of younger patients, with a median age at diagnosis of 34 years, whereas the median age at diagnosis of ALK-negative patients is 58. With the exception of the cutaneous vari ant and the variant associated with breast implants, most patients pres ent with rapidly growing lymphadenopathy with or without extranodal involvement; “B” symptoms are common. Most cases of ALCL involve large atypical lymphocytes with horse shoe-shaped nuclei with prominent nucleoli (“hallmark” cells). Tumor cells tend to be localized within the lymph node sinuses, and almost all are positive for CD30 but negative for CD15. A majority will also express CD3, CD25, CD43, and CD4. ALK-rearranged ALCL can be diagnosed by fluorescence in situ hybridization (FISH) cytogenetics for t(2;5) or by immunohistochemical staining for ALK. ALCL is generally treated with CHOP, although like PTCL NOS, CHOEP may benefit younger patients, particularly with ALK-positive disease. Overall, ALCL has a better prognosis than PTCL, and this is particularly true for ALK-positive disease, which has an 8-year OS rate of 82%, versus 49% for ALK-negative disease. Relapsed ALK-positive ALCL is treated similarly to relapsed DLBCL, with salvage combination chemotherapy to identify chemotherapy sensitivity followed by autolo gous stem cell transplant. For patients with chemotherapy-insensitive

disease or for ALK-negative disease, the conjugated anti-CD30 anti body to monomethyl auristatin E (MMAE)/brentuximab is highly active, with a response rate of 86% and a complete response rate of 57%. As mentioned earlier, brentuximab in combination with CHP chemotherapy is an approved frontline regimen for the treatment of CD30+ T-cell lymphomas, including ALCL. The ALK inhibitors, including crizotinib, are active in refractory ALK-positive ALCL with excellent outcomes.

Other PTCL Subtypes Enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma are other less common PTCL subtypes. Enteropathytype intestinal T-cell lymphoma is a rare disorder. Type I occurs in patients with a history of gluten-sensitive enteropathy and is associ ated with HLADQA1∗0501, DQB1∗0201; a gluten-free diet can pre vent the development of this lymphoma. Type II is now referred to as monomorphic epitheliotropic intestinal T-cell lymphoma and is not associated with celiac disease. Patients are frequently cachectic and sometimes present with intestinal perforation. The prognosis is poor, with a median survival of 10 months. Therapy is often with combina tion chemotherapy, including high-dose methotrexate, and autologous stem cell transplant in first remission. Hepatosplenic γδ T-cell lymphoma is a systemic illness that presents with sinusoidal infiltration of the liver, spleen, and bone marrow by malignant T cells. Tumor masses generally do not occur. The disease is associated with systemic symptoms and is often difficult to diagnose. Recurrent genetic events include isochromosome 7q and trisomy 8. Treatment outcome is poor, but regimens that include ifosfamide, such as ifosfamide, carboplatin, and etoposide (ICE) or ifosfamide, etopo side, and cytarabine (IVAC), are associated with better outcomes in small series of patients. Responding patients should be considered for allogeneic stem cell transplantation. CHAPTER 113 Non-Hodgkin’s Lymphoma Subcutaneous panniculitis-like T-cell lymphoma is a rare disorder that is often confused with panniculitis. Patients present with multiple subcutaneous nodules, which progress and can ulcerate. There is a more indolent form that tends to express α/β TCRs and can be man aged with immune suppression, whereas lymphomas that express γ/δ TCRs are more aggressive and are associated with a worse prognosis and coincident hemophagocytic syndrome.

This is a disease of young men in their fifth and sixth decades of life. Patients with aggressive disease are managed with multiagent chemotherapy, and responding patients should be considered for allogeneic stem cell transplantation. Adult T-Cell Leukemia/Lymphoma Adult T-cell leukemia/ lymphoma (ATLL) is a disease that is most prevalent in Japan and the Caribbean basin (Chap. 207). It is a neoplasm that is driven by HTLV-1,

often contracted through the breast milk of infected mothers. The average age at diagnosis is 60, so there is a long latency between viral infection and viral transformation, and only 4% of infected patients will develop the disease. This suggests that HTLV-1 may not be suffi cient to cause the malignant phenotype. There are four disease variants: acute (60% of patients), lymphomatous (20% of patients), chronic (15% of patients), and smoldering (5% of patients); prognosis varies across these groups, with median survival times of 6, 10, and 24 months, and not yet reached, respectively. Presentation depends on the subtype, but most commonly, patients present with circulating disease and bone marrow involvement, hypercalcemia, lytic bone lesions, lymphadenop athy, hepatosplenomegaly, skin lesions, and opportunistic infections. The pathognomonic finding is the malignant “flower cell” that is positive for CD4 and CD25, as well as CD2, CD3, and CD5 but lack ing CD7 (Fig. 113-7). Combination chemotherapy is generally used, but for patients fortunate enough to respond, response durations are very short. Other active agents in this disease include the antiretro viral agent zidovudine, interferon α, arsenic and mogamulizumab, a humanized monoclonal antibody that blocks the CCR4 chemokine receptor. In any patients who do respond to therapy, allogeneic stem cell transplant should be considered. Extranodal NK/T-Cell Lymphoma, Nasal Type Extranodal NK/T-cell lymphoma, nasal type, is a lymphoma that is associated with

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