Lymphoma

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KEYWORDS

• Lymphoma • Hodgkin • Non-Hodgkin • Diffuse large B cell • Follicular • Burkitt • MALT • T cell

KEY POINTS

- Symptoms and signs suggestive of lymphoma include fevers, drenching night sweats, unintentional weight loss, lymphadenopathy, and splenomegaly.
- PET/computed tomography scans are the preferred modality for imaging in most lymphomas and can help with both staging and identifying biopsy site.
- Excisional lymph node biopsy is preferred over needle biopsy.
- Aggressive lymphomas need urgent evaluation and treatment. Burkitt lymphoma is an oncologic emergency and requires emergent hospitalization and initiation of treatment.
- Long-term complications of chemotherapy and radiotherapy should be recognized during follow-up.

The incidence of lymphoma in the United States from 2009 to 2013 was approximately 22 in 100,000 people, representing 5% of malignancies.[1] Median age at diagnosis is 63. Between the 1970s and1990s, incidence doubled, but it has been stable since. Overall survival (OS), fortunately, is improving, and is now estimated to be 72% at 5 years.[1] The understanding of lymphomas represents a challenge for many, owing to a large number of subtypes and complex terminology.

Lymphomas are divided into Hodgkin (HL), 10%, and non-Hodgkin (NHL), 90% (**Table 1**).[2] HL is further divided into classical and nonclassical types, and NHL into B-cell and T-cell and natural killer (NK) cell types. For clinical purposes, it is worthwhile to keep in mind whether a given lymphoma is aggressive (high grade) or indolent (low grade). Most indolent lymphomas are NHL (with the exception of nodular lymphocyte predominant HL). Traditionally, indolent lymphomas are less dangerous if left untreated, yet, at the same time they are more difficult to cure. Although this may seem paradoxic, it is because the lower proliferation rate of indolent tumors makes them less susceptible to chemotherapy. The aggressive or indolent nature of the

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Table 1
Lymphoma subtypes with frequency

Lymphoma Subtype	Frequency (%)
Non-Hodgkin lymphoma	90
B-cell	
DLBCL	25–30
Follicular lymphoma	20
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	7
Chronic lymphocytic leukemia/small lymphocytic lymphoma	7
Mantle cell lymphoma	6
Burkitt lymphoma	1
Others	
Primary mediastinal large B-cell lymphoma	—
Primary effusion lymphoma	—
DLBCL associated with chronic inflammation	—
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma	—
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL	—
ALK-positive large B-cell lymphoma	—
Intravascular large B-cell lymphoma	—
Primary cutaneous follicle center lymphoma	—
Lymphomatoid granulomatosis	—
Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease	—
Plasmablastic lymphoma	—
Lymphoplasmacytic lymphoma	—
Splenic B-cell marginal zone lymphoma	—
Splenic B-cell lymphoma/leukemia, unclassifiable	—
Nodal marginal zone lymphoma	—
B-cell prolymphocytic leukemia	—
Hairy cell leukemia	—
T-cell/NK	9
Peripheral T-cell lymphoma, not otherwise specified	—
Angioimmunoblastic T-cell lymphoma	—
Extranodal NK/T-cell lymphoma, nasal type	—
Mycosis fungoides	—
Sézary syndrome	—
Anaplastic large-cell lymphoma, ALK positive	—
Anaplastic large-cell lymphoma, ALK negative	—
Enteropathy-type T-cell lymphoma	—
Hepatosplenic T-cell lymphoma	—
Subcutaneous panniculitis-like T-cell lymphoma	—
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders	—
Primary cutaneous peripheral T-cell lymphomas, rare subtypes	—

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Table 1
(*continued*)

Lymphoma Subtype	Frequency (%)
Epstein-Barr virus positive T-cell lymphoproliferative disease of childhood	—
T-cell prolymphocytic leukemia	—
Adult T-cell leukemia/lymphoma	—
T-cell large granular lymphocytic leukemia	—
Aggressive NK cell leukemia	—
Chronic lymphoproliferative disorders of NK cells	—
HL	10
Classical HL	10
Nonclassical HL	—

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; HHV, human herpes virus; NK, natural killer.

Data from National Institute of Health, National Cancer Institute. Available at: www.seer.cancer.gov/statfacts/html. Accessed May 8, 2016; and Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumors of hematopoietic and lymphoid tissues. 4th edition. Lyon (France): IARC Press; 2008.

lymphoma, along with a given patient's performance status, will define whether treatment is curative, where survival is the goal, or palliative, where quality of life is determinate. With indolent lymphomas, where cure is not an option, the most important treatment may be to avoid overtreatment, *primum non nocere*, "above all else do no harm." Of note, nonaggressive, indolent lymphomas can transform over time into aggressive lymphomas. Such transformation, called Richter's transformation when from chronic lymphocytic lymphoma, may be diagnosed upon first presentation (already transformed) or later in previously diagnosed low-grade disease.

For any given case of lymphoma, usually no underlying etiology is identified. That being said, a number of environmental, infectious, and genetic factors predisposing to lymphoma have been identified. Occupational exposure risks include herbicides and pesticides (including, notably, Agent Orange). A number of infectious organisms are associated with specific lymphomas, including *Helicobacter pylori, Borrelia borgdorferi, Chlamydia psittaci,* and *Campylobacter jejuni*. Human T-cell lymphotropic virus can lead to development of adult T-cell leukemia/lymphoma. Hepatitis C has been associated with lymphoplasmacytic and marginal zone lymphomas, and human herpes virus-8 with primary effusion lymphoma and Castleman disease. Chronic stimulation itself may predispose to development of lymphoma. Enteropathy-associated lymphoma is defined by the presence of underlying inflammatory bowel disease. Chronic antigen exposure occurs with persistent infections such as Epstein-Barr virus (EBV) and cytomegalovirus. There is also an increased incidence of lymphomas in most immunodeficiency states, including infectious (human immunodeficiency virus), iatrogenic (transplant), or genetic (severe combined immunodeficiency). Extranodal NK/T-cell lymphoma, nasal type, is increased in Southern Asia and parts of Latin America. Certain drugs affecting the immune system, such as tumor necrosis factor-alpha inhibitors, have also been associated with an increased incidence of lymphoma, in particular T-cell lymphoma.

A diagnosis of lymphoma is obtained by tissue biopsy, most often this having been facilitated by the primary care physician. In order of increasing amount of material

obtained, options for tissue biopsy include fine needle aspirate, core biopsy, incision/wedge biopsy, and excisional biopsy. Generally, the more tissue that can be obtained, the better. Indeed, the advantage of an excisional biopsy is that it allows for the assessment of whole lymph node architecture. When possible, it is best to obtain tissue where disease activity is greatest. PET/computed tomography (CT) scans, by measuring uptake of fluorodeoxyglucose, are an extremely useful indicator of the biologic activity of lymphoma.

The Ann Arbor Staging System (**Table 2**) was designed for HL, but is also used for NHL. The presence or absence of B symptoms, persistent fever, weight loss in excess of 10% of previous body weight over 6 months, or night sweats, are included in the staging for HL. Staging should be performed before the initiation of therapy. Basic blood work should include lactate dehydrogenase. Whole body PET/CT imaging is preferred over CT of the chest, abdomen, and pelvis for most lymphomas, with the exception of some low-grade lymphomas.[3] Bone marrow biopsy, with or without aspirate, is often performed for staging, but may be omitted for diffuse large B-cell lymphoma (DLBCL) and HL, because detection of stage IV over stage III disease with these lymphomas does not change treatment. In individual cases where a lymphoma is judged to be high risk, standard staging may be supplemented by cerebrospinal fluid testing.

The International Prognostic Index (IPI) was originally developed for diffuse DLBCL, but is used for most lymphomas.[4] Low IPI predicts a better outcome and high IPI a worse outcome (**Table 3**).[5] Further adaptation of the IPI may be found for specific lymphomas, for example, the FLIPI score for follicular lymphoma (FL) and the MIPI score for mantle cell lymphoma (MCL).

Antigen-specificity for B and T cells is defined by the cell-surface receptor, B-cell receptor or T-cell receptor, respectively. T cells are educated for antigen recognition in the thymus. B cells mature in the marrow and encounter foreign antigen for the first time within the lymph node germinal center (GC). As such, B cells may be divided into

Table 2
The Ann Arbor staging system

Stage	Definition
I	Involvement of 1 lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of 2 or more lymph node regions/structures on the same side of the diaphragm
III	Involvement of 2 or more lymph node regions/structures on different sides of the diaphragm
IV	Involvement of extralymphatic sites beyond that designated as "E," including more than 1 extralymphatic involvement of any location or any involvement of bone marrow/liver
A	No B symptoms
B	Unexplained fever of greater than 38°C on 2 or more occasions within 1 mo, drenching night sweats within 1 mo, and/or unintentional weight loss 10% or more of body weight within 6 mo
E	Localized, solitary involvement of extralymphatic tissue (excluding bone marrow/liver)

From Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7(11):1634–5.

Table 3
International prognostic index

Risk Factors
Age greater than 60 y
Elevated lactate dehydrogenase
Performance status 2 or higher (Eastern Cooperative Oncology Group) or 70 or greater (Karnofsky)
Stage III or IV
More than 1 extralymphatic site

Risk Category	No. of Risk Factors	4-y Overall Survival of Diffuse Large B-Cell Lymphoma (%)
Low	0–1	91
Low-intermediate	2	81
High-intermediate	3	65
High	4–5	59

Adapted from Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:991; and Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International Prognostic Index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:2377.

GC or post-GC. Post-GC, some B cells develop eventually into plasma cells, which secrete the soluble form of B-cell receptor, that is, immunoglobulin (Ig) or antibody. It is worthwhile to recall the physical structure of antibody, composed of 2 heavy and 2 light chains, each composed in turn of both variable and constant regions. It is the variable regions that determine antigen-specificity. For a given antibody, light chains may be of either kappa (κ) or lambda (λ) type. The most basic method for determining malignancy, or clonality, in B-cell lymphomas is by immunohistochemical (IHC) staining for light chains to demonstrate that a sample has lymphocytes expressing all kappa or all lambda light chains. This is referred to as light chain restriction and indicates the presence of a lymphocytic clone.

DIFFUSE LARGE B-CELL LYMPHOMA

DLBCL, an aggressive B-cell lymphoma, is the most common lymphoma, accounting for 25% to 30% of diagnoses (see **Table 1**). OS is about 60% at 5 years.[1] For most cases, no underlying etiology is identified. DLBCL arises most often within the lymph nodes, but presentation may also be outside of the lymphatic system, almost anywhere in the body. Indeed, DLBCL is the lymphoma most noted for extralymphatic presentation. The gastrointestinal tract is the most common site of extralymphatic presentation; testicular, ocular, and the central nervous system are other notable sites.

Histologic diagnosis includes the identification of areas of diffuse involvement by large lymphoid cells that stain positive for the B-cell marker CD20. Proliferation index, as determined by staining with the Ki-67 antibody, is expected to be moderate to high, albeit less than 100%.

Left untreated, survival in DLBCL is poor, but, fortunately, most DLBCL is chemosensitive. Treatment of DLBCL, therefore, is given with curative intent, performance status permitting. The gold standard for DLBCL treatment is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), with intravenous administration

occurring over 1 day. It is given as an outpatient and repeated every 3 weeks.[6,7] In most cases, 6 cycles of systemic chemotherapy are given.[8] For very localized disease, combination chemoradiation therapy may be chosen, with just 3 cycles of systemic chemotherapy supplemented instead by local radiation with the purpose of limiting overall exposure to systemic chemotherapy (at the expense, of course, of radiation).[9] For patients with poor performance status, milder treatment options may include R-mini CHOP (with reduced doses of all drugs except rituximab), R-CHOP minus doxorubicin (R-CVP), or single-agent rituximab.

The primary side effects of R-CHOP include nausea, fatigue, malaise, hair loss, and cytopenias. These are generally well-managed and considered to be tolerable with appropriate supportive care, in particular antiemetic medications. In some patients, progressive peripheral neuropathy from vincristine may be limiting. Particular attention should be paid to cardiac comorbidities owing to the cardiac toxicity of doxorubicin, an anthracycline. A baseline echocardiography or multigated acquisition scan before initiation of chemotherapy is recommended. Granulocyte colony stimulating factor may be used to support the white blood cell count.

Reimaging by PET/CT is recommended to assess for treatment response at the conclusion of treatment. Reimaging is most often also performed during treatment, after 2 to 4 cycles of chemotherapy, with the purpose of identifying those cases not responding to initial chemotherapy. Patients who complete successful therapy should be followed at regular intervals for the possibility of disease recurrence. Follow-up consists of history, physical examination, and basic laboratory tests (cell counts, electrolytes, creatinine, liver function tests, lactate dehydrogenase). Repeat imaging is not needed routinely, in the absence of specific concerns. Most disease relapse occurs within 2 years, such that the follow-up interval is increased if the disease remains in remission beyond 5 years.

Clinical trials are currently underway assessing the efficacy and safety of adding immunomodulatory agents (lenalidomide)[10,11] or Bruton's tyrosine kinase inhibitors (ibrutinib)[12,13] to R-CHOP in previously untreated DLBCL.

For patients who do not respond or relapse after first-line chemotherapy, several salvage regimens are available. Common second-line regimens (eg, R-ICE, R-DHAP) are also generally well-tolerated, albeit somewhat more intense than R-CHOP, and will commonly require in-patient administration to administer the chemotherapeutic agents. Survival after successful salvage therapy for resistant/relapsed DLBCL is improved significantly if salvage therapy is followed by high-dose chemotherapy with autologous stem cell rescue (HD-SCT).[14] The advantage of HD-SCT lies in the high dose of the chemotherapy. A harvest of autologous peripheral blood stem cells before administration of high-dose chemotherapy allows for the use of doses so bone marrow toxic that they would otherwise kill the patient, were it not for rescue by stem cell reinfusion. In cases where second-line therapies fail, clinical trials or allogeneic stem cell transplantation may be indicated.

FOLLICULAR LYMPHOMA

FL, an indolent B-cell lymphoma, accounts for 20% of diagnoses, making it the second most common lymphoma (see **Table 1**). Median OS is 8 to 15 years, depending on extent of disease at diagnosis.[1] Presentation is most often with diffuse lymphadenopathy, but disease may also be localized or occasionally extralymphatic.

By definition, the cell of origin counterpart for FL is the follicular cell of the GC. In contrast with noncancerous follicular cells, in which the antiapoptotic protein Bcl-2 is downregulated (to allow for the cell turnover that occurs in the GC during an immune

response), in FL cells, Bcl-2 is overexpressed. This overexpression is the result of translocation of the BCL-2 gene site (normally found on chromosome 18) to the B-cell receptor or Ig gene site (chromosome 14), namely t(14;18), found in almost all cases of FL. Like DLBCL therefore, FL is a GC-derived B-cell lymphoma. In some cases, FL may transform into DLBCL.

A histologic diagnosis of FL classically includes the identification within the lymph node of areas of considerable follicular proliferation and expansion. Within expanded follicules, in turn, small and large cells proliferate (just as in a reactive lymph node), but, rather than being a mix of B cells ($CD20^+$) and some T cells ($CD3^+$), in FL, the follicles are composed mostly of B cells positive for Bcl-2. There is, in FL, however, as in a reactive node, variation in actual size among follicle B cells, small cells called centrocytes and large cells centroblasts. The proportion of large cells, centroblasts, is reported as being either greater than, or less than, 15 cells per high-power field. The more large centroblasts, the higher the grade; in grades I and II there are 0 to 15 centroblasts per high-power field, whereas in grade III there are greater than 15 centroblasts per high-power field. The difference between FL grade IIIA and grade IIIB is the presence of a mixture of centrocytes and centroblasts in all follicles in grade IIIA versus the presence of follicles composed exclusively of centroblasts, immunoblasts (activated lymphocytes), or both, in grade IIIB. Of note, FL grade IIIB is managed as if it were DLBCL.

Prognosis in FL is predicted by the FLIPI score. As an indolent lymphoma, the clinical behavior of FL is variable. Some cases of FL remain asymptomatic, even untreated, or wax and wane on their own, whereas others progress and cause significant symptoms. Asymptomatic FL can be managed by watchful waiting, that is, monitoring for appearance of progression or significant symptoms before intervening. Median OS is measured in decades, such that often the diagnosis of FL does not impact life span. Treatment is generally not considered to be curative, so it must be chosen judiciously, weighing benefit against toxicities and keeping in mind that, after multiple therapies, toxicity will be cumulative. Some patients are uncomfortable with a watch and wait strategy because they feel that they are not receiving any treatment and will need counseling to understand that observation, in this case, is a form of treatment.

For localized FL confined to 1 lymph node area, radiotherapy may be chosen as the sole modality of therapy. More frequently, however, several areas within the body are involved in FL, and systemic therapy is needed. Often, a less aggressive approach, such as single-agent rituximab, may be chosen as first-line therapy, even for patients with good performance status, thus reserving the option of escalation in therapy for future need. For higher burden FL, it may be necessary to start with systemic cytotoxic chemotherapy. In FL, a number of different regimens have been used over the years. Since OS in FL is measured in decades, it has been difficult to demonstrate superiority of 1 regimen over another. Nevertheless, in recent years, rituximab-bendamustine (R-benda) has emerged as the most popular treatment, being superior to R-CHOP in terms of progression-free survival.[15] R-benda is usually given over 2 consecutive days as an outpatient, repeated every 4 weeks for 6 cycles. Side effects of this anthracycline-free drug are usually less than with R-CHOP, but leukopenia may be prolonged. Maintenance rituximab after completion of front-line systemic chemotherapy, usually once every 2 months for 2 years, has been shown to prolong progression-free survival but not OS.[16] As an incurable disease, relapse of FL is anticipated at some point, but can usually be treated with one of the other regimens available for frontline treatment. Upon recurrence of all indolent lymphomas, one should exclude the possibility of the transformation to aggressive lymphoma. In cases of early

FL relapse or other aggressive features, HD-SCT or allogeneic transplantation may be considered.

EXTRANODAL MARGINAL ZONE LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE

Normal mucosal tissue includes small lymphocytic aggregates dispersed in a noncontinuous fashion, known as mucosa-associated lymphoid tissue (MALT). These aggregates may proliferate during an immune response to form reactive follicles. Lymphoma that arises from the marginal zone of such aggregates is called MALT lymphoma, and accounts for about 7% of all lymphomas.[1] MALT lymphoma is an indolent B-cell lymphoma. OS survival is excellent, and there is less of a tendency to recur than with FL. Often disease is limited to local involvement, although multiple extranodal involvement and disseminated disease forms do exist. Repeated local antigen stimulation in the context of infections, autoimmune disease, or other inflammatory conditions may predispose to development of MALT. Well-documented associations include *H pylori* (gastric), *C psittaci* (ocular), *C jejuni* (small intestine), *B borgdorferi* (skin), as well as Hashimoto thyroiditis (thyroid) and Sjögren syndrome (salivary). Cell of origin is the marginal zone cell, a post-GC B-cell. Diagnosis is made by identifying aggregates of small lymphocytes with appropriate IHC staining profile ($CD20^+$ with a so-called null-phenotype, $CD10^-$ $CD5^-$).

In some cases, removal of the provocative agent may be sufficient treatment. In gastric MALT lymphoma, successful eradication of *H pylori* can often lead to full tumor regression, and this is therefore recommended as the first step in treatment (in cases of t(11;18) positive gastric MALT, *H pylori* eradication alone is insufficient).[17] An indolent disease, MALT lymphoma is treated with the same approach as discussed for FL, from watchful waiting to systemic cytotoxic chemotherapy, depending on the stage and clinical behavior.

MANTLE CELL LYMPHOMA

MCL, which comprises about 6% of lymphomas,[1] is often said to combine the worst characteristics of both the low- and high-grade lymphomas, namely, the incurability of low-grade lymphomas with the aggressive nature of high-grade lymphomas. Indeed, outcome for MCL is among the worst of all lymphoma subtypes; median OS is about 5 years.[1] That being said, MCL actually represents a wide spectrum of disease, with some patients, particularly elderly, who exhibit a very indolent course, allowing even just for observation without any treatment. The etiology is unknown, although there is a male predominance. MCL usually presents with widespread disease, most often with bone marrow involvement. Another common site of disease is the gastrointestinal tract. Multiple polyps, a condition known as lymphomatous polyposis, may cause gastrointestinal obstruction. Cell of origin, as the name suggests, is believed to be the mantle zone cell of the lymph node, that is, a post-GC B cell. The diagnosis is made by recognizing areas of small lymphoid cells, in some cases arising directly from an expanded mantle zone, with characteristic IHC staining and essentially always positive for cyclin D1, a protein involved in cell cycle regulation. The latter results from the translocation of the gene encoding for cyclin D1 on chromosome 11 and that encoding for Ig on chromosome 14, namely t(11;14). Prognosis in MCL is predicted by IPI score or, more selectively, by MIPI score.

Treatment for older patients with less aggressive disease may be with R-benda (or R-CHOP),[15] followed by maintenance rituximab.[18] Most patients, however, require more intensive regimens. One agent, cytarabine, is found in most regimens, because

it has particular activity in MCL. Often, front-line chemotherapy is followed directly in first remission by consolidation with HDC-SCT. One such approach is the Nordic protocol (a maxi R-CHOP regimen alternating with rituximab-cytarabine).[19] Another regimen is alternating hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) with methotrexate/cytarabine.[20] Lenalidomide and bortezomib have single-agent activity in relapsed MCL[21,22] and have recently been added to combination treatments for newly diagnosed MCL.[23,24] The Bruton's tyrosine kinase inhibitor, ibrutinib, has excellent activity in MCL and is approved by the US Food and Drug Administration for use in relapsed MCL.[25]

BURKITT LYMPHOMA

Burkitt lymphoma (BL) was first described by the Irish surgeon Denis Burkitt in 1958, and is a highly aggressive B-cell lymphoma. There are 3 forms of BL—endemic, spontaneous, and immunodeficiency associated. Endemic BL is the form recognized by Denis Burkitt while working as a missionary in Uganda and is a pediatric tumor typically presenting as a mandibular mass. It is the endemic form of BL that is most strongly associated with EBV infection; almost no cases occur in the absence of chronic infection. In North America, the most common form of BL is the spontaneous form. This form often presents as an abdominal mass. Immunodeficiency-associated BL is seen above all in human immunodeficiency virus infection; its presence, indeed, can be an AIDS-defining condition.

Molecularly, the pathogenesis of BL is driven by a translocation of the notorious cell proliferation protooncogene, C-MYC, to one of the sites encoding for Ig expression, either the heavy chain or one of the 2 light chains, κ or λ, respectively t(8;14), t(2;8), or t(8;22).

The diagnosis of BL is made by recognition of medium to large B cells with extremely high proliferation rate (Ki-67 essentially 100%), manifesting histologically as the classic starry sky appearance, a result of tingible-body macrophages with surrounding clearing.

BL should be approached as an oncologic emergency owing to a high proliferation rate of the tumor. This high proliferation rate necessitates immediate treatment with aggressive chemotherapy regimens in which the intensity of delivery is meant to outpace the capacity for cellular division to prevent development of tumor resistance. Failure to do so can result in rapid tumor proliferation, end-organ damage, and death. If treatment is initiated in a timely manner, however, results can be favorable. Treatment options for BL include R-hyperCVAD-methotrexate/cytarabine[26] and R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, cytarabine).[27,28] Recently, DA-R-EPOCH, a regimen that is intense yet easier to tolerate than the others named, has shown promise.[29,30] With BL, obtaining a good response with the first attempt at treatment is considered to be of particular importance.

T-CELL LYMPHOMAS

T-cell and NK cell lymphomas include a diverse group of lymphomas that together account for only 10% of NHL, compared with the 90% that are B-cell lymphomas. It is only in recent years that T-cell lymphomas have been more reliably subtyped. The most frequently diagnosed T-cell lymphoma, however, remains the peripheral T-cell lymphoma not otherwise specified, a diagnosis of exclusion. Systemic chemotherapy used for T-cell lymphoma is in general similar to that used for aggressive B-cell NHL, save for the exception of rituximab (anti-CD20, a B-cell marker). Overall outcomes for

T-cell lymphomas are inferior to B-cell lymphomas. For CD30 positive T-cell lymphomas, an antibody–drug conjugate, brentuximab, has been effective.[31] Histone deacetylase inhibitors such as romidepsin and belinostat have modest activity in T-cell lymphoma.[32–34]

HODGKIN LYMPHOMA

HL accounts for 10% of lymphomas (see **Table 1**).[1] First identified by the British pathologist Thomas Hodgkin in 1832, HL is defined by the presence of pathologic Hodgkin Reed-Sternberg (HRS) cells, now known to be of B-cell origin. Similar to NHL, HL contains both aggressive and indolent forms, although classic HL, which is aggressive, accounts for 95% of cases. Morphologically, classical HL has been divided into 4 distinct variants, in decreasing order of frequency—nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted. Today, however, all of the variants are managed similarly. Nonclassical HL, on the other hand, of which only 1 type exists—nodular lymphocyte predominant—is indolent and is managed differently, often with radiation only.

The incidence distribution of HL is bimodal. There is 1 age peak in the early 20s and a second in the mid 60s. For most cases, no underlying etiology is identified. In some subtypes of classical HL, a significant number of cases are positive for EBV, leading to speculation that EBV may play a causative role, but this remains to be proven. Some genetic predisposition to HL is suspected, because there is an increased relative risk among relatives of patients. Environmental factors are also suspected, with increased incidence among woodworkers, farmers, and meat processors. The incidence of HL is increased in patients with immunodeficiencies.

The primary care physician should be suspicious of young patients presenting with painless lymphadenopathy, with or without B symptoms. HL most often arises from within the lymph nodes, and frequently presents with B symptoms. The pattern of spread is often contiguous through successive lymph node stations. Some patients may complain of itching with no rash, and others of pain in involved lymph nodes after drinking alcohol. Histologically, the diagnosis of HL is made by identifying HRS cells, odd-looking large, bilobed cells often with 2 nuclei, appearing within a background of nonmalignant inflammatory cells. Determining B-cell lineage of the HRS cell was difficult, because IHC staining of several key markers in classical HL ($CD20^-$ $CD30^+$ $CD15^+$) is exactly opposite that expected for B cells. Left untreated, survival in classical HL is poor. Fortunately, however, most cases are highly chemosensitive and OS, at 86%, is very good.[1] Within the lymphoma field, HL is the showcase example of the effectiveness of modern chemotherapy.

Standard treatment in the United States and most other countries consists of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).[35,36] In Germany, the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) has been popular.[37] Another regimen used is Stanford V (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, prednisone).[38] Response rates to these regimens are similar, with BEACOPP giving slightly better cure rates than the other 2, but at the cost of a greater toxicity, including development of secondary acute myeloid leukemia/myelodysplastic syndrome, and, in particular, sterility, a side effect almost unseen with ABVD. In a relatively young population, sterility is naturally of major concern to patients.

ABVD requires intravenous administration over 1 day on alternate weeks, twice for each cycle. If disease is widespread (Ann Arbor stages III–IV), generally 6 cycles of ABVD are administered. For localized disease (Ann Arbor stages I–II), 2 to 4 cycles

are usually preferred, depending on presence or absence of any unfavorable features: B symptoms, bulky mediastinal or greater than 10 cm disease, erythrocyte sedimentation rate of 50 or greater, or more than 3 sites of disease. Systemic chemotherapy may be supplemented by local radiation, either because of bulky disease or persistent PET/CT positivity after chemotherapy. Primary side effects of ABVD include a decrease in blood counts, nausea, malaise, fatigue, and hair loss, as well as peripheral neuropathy. These may be significant but can generally be managed acceptably. Baseline echocardiography or multigated acquisition are performed before initiation of treatment owing to the use of doxorubicin. Pulmonary toxicity of bleomycin is a concern, requiring baseline pulmonary function testing and monitoring for onset of any symptoms along the way.

Repeat imaging is recommended to assess for treatment response. HL is particularly PET/CT avid, so this modality is recommended. PET/CT results are judged by Deauville criteria, whereby signal less than (or equal to) the physiologic signal from the liver is negative (1–3) and signal greater than liver (4–5) is positive. Today, a strategy evolving in both the United States and Europe is to initiate treatment with ABVD, monitor response with repeat PET/CT after 2 cycles, and to escalate treatment to BEACOPP only for those patients with inadequate response.[39–44] Furthermore, recent indications are that if PET/CT response to ABVD is good, then bleomycin may be omitted from later cycles without compromising response, and sparing unnecessary pulmonary toxicity.[45]

Upon completion of therapy, patients require follow-up at regular intervals to exclude disease recurrence, again with only history and physical and basic laboratory tests, but without routine repeat imaging. Because many patients with HL are young and cured, they will live for a long time after treatment and must be monitored for late sequelae of treatment, in particular for the development of secondary cancers within previous radiation fields, such as lung, breast, or thyroid, as well as coronary artery disease.

For those patients with relapsed or resistant HL, several salvage regimens are available. Specifics are beyond the scope of this article, but 1 agent frequently preferred in this setting is brentuximab, a monoclonal antibody to CD30, one of the molecules for which HRS cells are distinctively positive, coupled to an antimitotic spindle apparatus agent, monomethyl auristatin. As of today, brentuximab is approved by the US Food and Drug Administration for HL as a second-line agent only,[46] but trials are underway using brentuximab upfront in ABVD, in place of bleomycin.[47] Salvage therapy in HL, if successful, may be followed by consolidation with HD-SCT. Where disease is fully resistant or relapses again after HD-SCT, experimental agents within the context of a clinical trial are indicated, or, in selected cases, allogeneic stem cell transplantation. Nivolumab and pembrolizumab, programmed death-1 inhibitors, have shown remarkable overall response rates (up to 87%) in refractory HL in phase I trials.[48–50]

SUMMARY

It is important for the primary care clinician to recognize the symptoms and signs that are suggestive of lymphoma: fevers, drenching night sweats, unintentional weight loss, lymphadenopathy, and splenomegaly. Diagnosis of lymphoma is made on biopsy. Excisional biopsy is preferred because it allows for examination of whole lymph node architecture. Lymphomas may be grouped into NHL and HL. Treatment options of chemotherapy and radiotherapy vary by histologic subtype. Clinically, the most important distinction is to recognize whether a given lymphoma is of an indolent or aggressive nature. Aggressive lymphomas are more dangerous if left untreated, yet,

a higher cell proliferation rate renders them more chemosensitive. As such, aggressive lymphomas are managed with curative intent, and need urgent evaluation and treatment. Indolent lymphomas, in contrast, are in general incurable, so quality of life must be balanced against toxicity of treatment when determining if and how to treat them.

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