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EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Differentiate the two large groups of non-Hodgkin lymphoma
- Describe the diagnostic methods used in tumor identification
- Discuss the basic treatment options for non-Hodgkin lymphoma

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Differentiating type is key to non-Hodgkin lymphomas

Donald R. Fleming, MD

STATEMENT OF NEED/PROGRAM OVERVIEW

The most important factor to consider in the treatment of patients with non-Hodgkin lymphoma (NHL) is the type of lymphoma. Some types require prompt treatment for a complete response, whereas some types are treated as a chronic disease. Although there are dozens of different types of lymphoma, most disease is within a select number of types. Treatment protocol is to match the aggressiveness of treatment with the grade of disease, which minimizes the potential for under- and overtreatment.

CE INFORMATION

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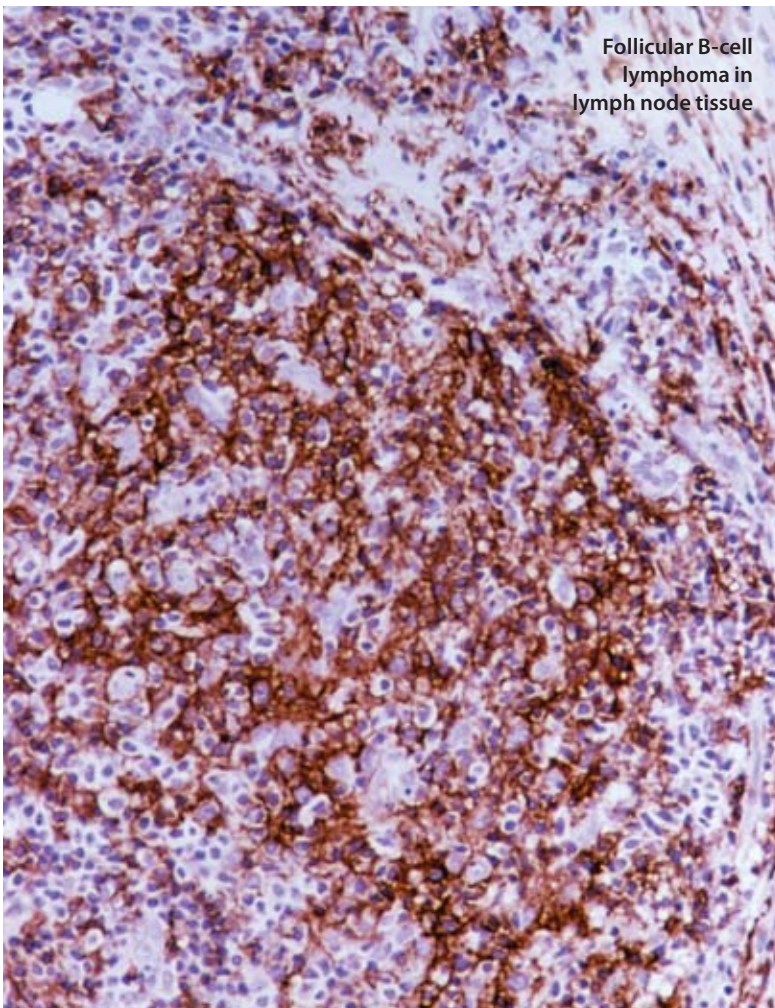
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Differentiating type is key to non-Hodgkin lymphomas

Management and prognosis for patients with NHL depend on identifying the disease type. This review discusses the diagnoses and optimal treatments.



Follicular B-cell
lymphoma in
lymph node tissue

DONALD R. FLEMING, MD

The name *non-Hodgkin lymphoma* (NHL) implies a diagnosis ancillary to Hodgkin lymphoma, which is also known as *Hodgkin disease*. However, the incidence of NHL is several times that of Hodgkin disease and has doubled since the early 1970s. Risk factors are primarily associated with an immune system deficiency or a history of immunosuppressive therapy. Although the higher incidence can be attributed to improved diagnostic techniques and increased access to medical care, environmental factors and the increasing median age of the population are contributors. Toxins related to chemicals used in the farming industry also occasionally increase incidence of NHL.¹

Non-Hodgkin lymphoma represents approximately 5% of all malignancies. NHL is the fifth most common cancer among both men and women, with a slight predominance in men. The only patient population to experience a decrease in incidence of NHL is young males, primarily because of improved treatment for HIV infections and subsequent lower incidence of associated lymphoma with HIV progression.

DIAGNOSIS

Patients with NHL may present with fever, weight loss of 10% or more, and night sweats; these symptoms are also known as *B symptoms*.

Many indolent types of lymphoma manifest with only painless swelling of the lymph nodes. After NHL is diagnosed, patients often undergo a litany of procedures such as extensive evaluation for peripheral lymphadenopathy, hepatosplenomegaly, various imaging studies (most often positron emission tomography [PET] and CT, but other imaging studies may be needed), and bone marrow aspiration and biopsy.

The primary diagnosis is made via molecular testing of a resected lymph node specimen, the most informative of which is flow cytometry. Another diagnostic tool, especially for cases of the more rarely occurring T-cell lymphomas, is PCR (polymerase chain reaction) for antigen receptor rearrangements (PARR). These tests determine whether the specimen cells are derived from a single cell line or from what is typically referred to as *clonality*.¹⁻³ Clonality is the hallmark of malignancy and manifests as all cells having the same sequence of nucleic acid or DNA (monoclonal expressions). Nonmalignant tissue has polyclonal expressions. PARR studies evaluate the T-cell receptor gene variable region in T-cell lymphomas, whereas the variable regions of the immunoglobulin receptor gene is evaluated in B-cell lymphomas. As implied by the name, the variable region by nature should vary in order to mount unique responses to unique antigens, and the loss of this variability implies a malignancy exists. PARR studies amplify the abnormal variable region of the clonal population in B-cell lymphomas.

Flow cytometry is more commonly used because the technique is the most important study for analyzing lymphoma-involved tissue, usually lymph node or bone marrow. A solution with the malignant tissue is treated with various fluorochromes and antibodies and passed through a laser beam. The laser recognizes and sorts out the cells based on size, DNA content, and antibody reactions. A pattern that identifies the lymphoma develops as the receptors are labeled. Each type of lymphoma produces a distinct “fingerprint” based on the cluster differentiation (CD) positivity that occurs within the panel. The various CD types are designated by numbers; for example, CD20 is very often expressed on individual B-cell lymphoma cells.^{2,3}

TYPES OF LYMPHOMA

The most important factor in diagnosing NHL is identifying the type of non-Hodgkin lymphoma. Although most normal circulating lymphocytes are T lymphocytes, 85% of NHL clonality involves B lymphocytes versus 15% for T-cell lymphomas.

In the 1970s, the National Cancer Institute (NCI) designed a working classification for the NHLs. Previous attempts at organizing the various NHL types were very difficult because many institutions had their own preferred classification system.

The NCI classification designated lymphomas based on the clinical aspects of the disease and subcategorized NHLs as indolent, intermediate, and aggressive types, often designated as low-, intermediate-, and high-grade, respectively. Much of this work was accomplished prior to the widespread use of flow cytometry and PARR. When these molecular techniques became available, they were incorporated into the working classification. Thus, the Revised European American Lymphoma (REAL) classification system was developed, which more precisely identified the various types of NHL.¹⁻³

Although there are literally dozens of NHL types, most disease are within a select number of types (Table 1).¹⁻³ Follicular lymphoma is the most common low-grade type. Diffuse large B-cell lymphoma, an intermediate-grade type, is the most common of all lymphoma types. High-grade lymphomas are usually either Burkitt lymphoma or lymphoblastic B-cell type lymphoma; the latter has a morphology similar to acute lymphoblastic B-cell leukemia. Human herpesvirus 8 (HHV-8)-associated primary effusion lymphoma, a virally associated lymphoma type, was most prevalent in HIV-infected persons prior to the advent of highly active antiretroviral therapy (HAART) for HIV infection.¹⁻³

Most T-cell lymphomas also are designated as low-, intermediate-, and high-grade types.¹⁻³ The most common cutaneous T-cell lymphoma is mycosis fungoides, a low-grade

Staging is an important assessment in all malignancies; however, accurate identification of subtype is paramount in NHLs.

type. T-cell lymphoblastic lymphoma, which is a high-grade disease, is akin to a T-cell type of lymphoblastic leukemia. Human T-cell lymphoma virus (HTLV)-associated aggressive leukemia/lymphoma, a virally associated lymphoma, often affects Caribbean or Asian populations.¹⁻³

In addition, some types of lymphoma have no designation, including a prelymphomatous condition known as lymphomatoid papulosis, some cutaneous and subcutaneous T-cell types of lymphomas, large B-cell lymphoma of the skin, and large B-cell lymphoma of the leg. These unique lymphoma types are rarely seen and have profound cutaneous presentations. They are mentioned here for the sake of completeness.

DISEASE STAGING

Similar to most cancers, lymphomas are staged as I, II, III, or IV disease. Unlike solid tumors, however, staging is less

significant in NHLs as most cases involve more advanced disease. The treatment, primarily chemotherapy, is universally distributed and effective in managing the disease process. Staging of non-Hodgkin disease is a by-product of evaluating Hodgkin disease; however, unlike Hodgkin disease, NHL seldom progresses from one lymph node to the next nearest one in a contiguous spreading fashion. Therefore, staging has less applicability to NHL. Nevertheless, the Ann Arbor staging technique devised for Hodgkin disease has been applied to NHL.

The Ann Arbor technique designates stages I and II as one disease site and more than one lymph node site, respectively, on the same side of the diaphragm. Stage III involves multiple lymph node sites on both sides of the diaphragm. Stage IV disease includes extranodal involvement in the liver, the lungs, or most commonly, the bone marrow. Certain clinical and laboratory parameters combined with staging provide better prognostic information for patients with NHL compared with information from staging alone.

The International Prognostic Index (IPI) score was initially developed for more aggressive lymphomas and was followed by the Follicular Lymphoma International Prognostic Index (FLIPI) score for the second most common form of lymphoma⁴⁻⁶ (Table 2).

TREATMENT

The nearly universal expression of the CD20 receptor on B-cell lymphomas is a target of rituximab (Rituxan) therapy. Rituximab is a monoclonal antibody that binds to the CD20 receptor. Although the agent is effective as a single agent to treat various types of B-cell lymphomas, it is often used in conjunction with chemotherapy to increase its efficacy.

A variety of therapeutic options have been used to treat low-grade B-cell lymphomas. The generally accepted goal of treatment is to control the disease, not cure the patient because these patients are often elderly and have numerous comorbidities. The risks inherent with the only curative approach, allogeneic stem cell transplant, have a higher

TABLE 1. Non-Hodgkin lymphoma types

Type	Examples
B-CELL LYMPHOMAS	
Low-grade (indolent)	<ul style="list-style-type: none"> • Follicular lymphoma • Lymphoplasmacytic lymphoma (also known as Waldenström macroglobulemia) • Marginal zone lymphoma (such as primary splenic lymphoma and MALT lymphoma) • Small lymphocytic lymphoma
Intermediate-grade (intermediate)	<ul style="list-style-type: none"> • Diffuse large B-cell lymphoma • Mantle cell lymphoma • Small noncleaved-cell non-Burkitt lymphoma
High-grade (aggressive)	<ul style="list-style-type: none"> • Burkitt lymphoma • Lymphoblastic B-cell lymphoma
Virally associated	HHV-8 associated primary effusion lymphoma
T-CELL LYMPHOMAS	
Low-grade (indolent)	<ul style="list-style-type: none"> • Cutaneous CD30+ anaplastic large cell lymphoma • Cutaneous T-cell lymphoma • Large granular lymphocytosis
Intermediate-grade (intermediate)	Extracutaneous anaplastic large cell lymphoma
Peripheral T cell	<ul style="list-style-type: none"> • Angioimmunoblastic lymphoma • Hepatosplenic lymphoma • Intestinal lymphoma • Nasopharyngeal lymphoma • Peripheral T-cell lymphoma, not otherwise specified • Primary subcutaneous
High-grade (aggressive)	T-cell lymphoblastic lymphoma
Virally associated	HTLV-1 leukemia/lymphoma
Key: HHV-8, human herpesvirus type 8; HTLV, human T-cell lymphoma virus; MALT, mucosa-associated lymphoid tissue.	

mortality rate than the disease. Rituximab combinations with chemotherapeutic agents are the mainstay of therapy. Until recently, the chemotherapy regimens used most often were R-CVP (rituximab plus cyclophosphamide [Cytoxan, Neosar, generics], vincristine [Oncovin, Vincasar, generics], prednisone) and R-CHOP (rituximab plus cyclophosphamide, doxorubicin [hydroxydoxorubicin, Andriamycin, Doxil, Rubex, generics], vincristine [Oncovin], and prednisone). However, bendamustine (Treanda), a recently marketed chemotherapy agent, plus rituximab has the same efficacy as R-CHOP with less toxicity.⁷⁻¹⁰ An equally debatable issue is when to treat low-grade B-cell lymphomas.

No studies have demonstrated that treating the disease before the patient becomes symptomatic or excessive marrow involvement is apparent (such as development of anemia and thrombocytopenia) results in better patient outcomes. However, the opposite is true for diffuse large B-cell lymphoma. The gold standard for achieving a complete remission is treatment with R-CHOP as early as possible, as untreated disease has a definitive impact on patient survival. Approximately 30% of patients who experience a relapse will require extremely high doses of chemotherapy and radiation followed by a stem cell transplant. Using an autologous source of stem cells most often minimizes the complications following transplant.¹¹

Mantle cell lymphoma has the worst characteristics of both low-grade lymphomas and large B-cell intermediate-grade lymphomas. Similar to low-grade lymphomas, mantle cell lymphoma cannot be cured; and the same as large B-cell intermediate-grade lymphomas, it has a fairly rapid and pernicious course. Treatment is quite controversial; R-CHOP alone is not found to be adequate. Use of higher-dosage chemotherapy regimens with or without autologous stem cell support has been met with resistance. An aggressive form of B-cell lymphoma therapy involves regimens of conventional chemotherapy administered with rituximab and higher doses of cyclophosphamide in conjunction with cytarabine (Cytosar-U, DepoCyt), referred to as R-hyper-CVAD (rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone [Decadron, Dexamethasone Intensol, Dexpak Taperpak, generics]).¹

T-cell lymphomas have a much lower incidence; therefore, the pharmaceutical industry has much less focus on this form of lymphoma. Patients with low-grade forms of T-cell lymphomas have benefited from treatment interventions ranging from topical agents to systemic approaches with chemotherapy and biologic therapies.¹²

The intermediate forms of T-cell lymphoma are primarily treated with CHOP-like regimens without rituximab, as

TABLE 2. Prognostic risk factors

International Prognostic Index (IPI)
≥2 extra-nodal sites of involvement
Age >60 y
Ann Arbor stage III or IV
ECOG performance status ≥2 or equivalent
Serum LDH level higher than normal
Follicular Lymphoma International Prognostic Index (FLIPI)
>4 nodal sites
Age >60 y
Ann Arbor stage III or IV
Hemoglobin level <120 g/L
Serum LDH level higher than normal
Note: Low risk, 0-1 factors; intermediate risk, 2-3 factors; high risk, 4-5 factors Key: ECOG, Eastern Cooperative Oncology Group.

these lymphomas do not express the CD20 receptor.^{13,14} A new anti-CD30 monoclonal antibody, known as brentuximab vedotin, seems to be highly effective and may become the “rituximab” for this type of lymphoma.¹⁵ The peripheral T-cell lymphomas (PTCLs) are grouped together in therapeutic interventions, and treatment with CHOP-like regimens has limited success as these patients often relapse. The most effective treatment options are high doses of chemotherapy with or without radiation, followed by either autologous or allogeneic stem cell transplant. Recently a new chemotherapeutic agent, pralatrexate (Folotyn), has demonstrated effectiveness in treating patients with PTCL relapse.¹⁶

High-grade T-cell lymphomas are often managed in a similar manner as their aggressive B-cell counterparts. Unfortunately, not much success has been achieved in treating the virally associated HTLV lymphoma, which is highly refractory to various treatments.

CONCLUSION

Although disease staging is an important assessment in all malignancies, an accurate identification of subtype is paramount in management of the disease process of NHLs. Various classification systems are established based on the aggressiveness of the disease type, and maintaining clinical application of these systems is useful. Typically, more aggressive therapeutic interventions are matched to high-grade

disease; therefore, the potential for over- or undertreatment of the disease is minimized. ■

Donald Fleming is an oncologist at the Cancer Care Center, Davis Memorial Hospital, Elkins, West Virginia, and a member of the *Oncology Nurse Advisor* editorial board.

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