

Clinical Perspectives on Lymphoma in Managed Care: Diagnosing, Staging, and Treatment

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Lymphoma accounts for more than half of all new hematological malignancies,

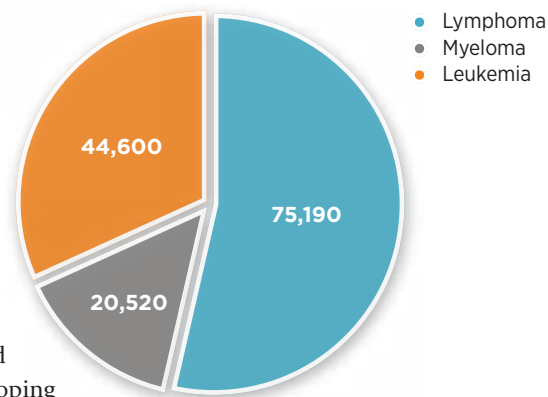
making it the most prevalent blood cancer and a leading cancer type overall in terms of U.S. incidence (Figure 1).¹ It is estimated that more than 88% of lymphoma cases are attributable to non-Hodgkin lymphoma (NHL), representing the seventh most common cancer site in the U.S.¹ Furthermore, NHL is expected to result in more than 19,000 deaths in 2011, ranking eighth among all cancer sites.¹ Although NHL and Hodgkin lymphoma each accounts for

4% of all pediatric cancers, more than 95% of NHL cases occur in adults.^{1,2}

In fact, the average age at diagnosis

of NHL is in the 60s, and approximately half of patients diagnosed with NHL are 65 and older. As such, the risk of developing NHL increases throughout life, which will likely result in increasing NHL prevalence as the U.S. population ages in the coming years.² In addition – despite this elevated incidence in the elderly – NHL's demonstrable occurrence across the continuum of plan-member age groups highlights the importance of effectively

Figure 1. Estimated New Cases of Selected Hematological Malignancies, 2011¹



diagnosing and treating the disease in managed care.

Beyond age, the likelihood of being diagnosed with NHL is affected by gender and race. NHL is more prevalent in males, and the probability of developing NHL is greater among males than females at any age.¹ In terms of

race, African-Americans have higher incidence rates of NHL than whites from the mid- to late teen years to the mid-50s.³ Beginning at age 55, however, whites generally have considerably higher incidence rates of NHL.³

Regardless of age, gender, or race, NHL represents a varied array of diseases that are distinguished by the characteristics of the cancer cells unique to each type. The “non-Hodgkin” designation was originally introduced by the Working Formulation in 1982, which recognizes 16 different forms of lymphoma that have little in common with one another outside of the absence of Reed-Sternberg cells exclusive to Hodgkin lymphoma.³ While the latest lymphoma classification – the 2008 World Health Organization classification – largely abandons the “Hodgkin” vs. “non-Hodgkin” grouping and instead lists more than 70 different forms of lymphomas, the Working Formulation and the NHL category continue to be used by major cancer agencies, including the National Cancer Institute’s SEER (Surveillance Epidemiology and End Results) program and the National Comprehensive Cancer Network.⁴ Among the 16 forms of NHL originally recognized by the Working Formulation, the designations “indolent” or “aggressive” may be applied to indicate more or less favorable prognostic factors, respectively. However, in order to adequately assess prognosis, individual cases of NHL must be first diagnosed and staged according to specific criteria.

DIAGNOSIS AND STAGING

NHL may cause different signs and symptoms in patients depending on the specific type or the disease’s location in the body. In many cases,

symptoms do not surface until the cancer has spread or grown to a considerable extent. In general, a patient with NHL may present with the following symptoms: enlarged lymph nodes, swollen abdomen, chest pain or pressure, shortness of breath, coughing, fever, weight loss, night sweats, and fatigue. More specifically, in patients with B-cell NHL – the most common, albeit heterogeneous, form of the disease – symptoms may include fever, chills, night sweats, weight loss, asymmetrical lymph node enlargement, and neurologic pain resulting from visceral lymph involvement.

When the aforementioned symptoms indicate the potential presence of NHL, patients must undergo further evaluation for a definitive diagnosis; specifically, a biopsy is necessary. And while a fine needle aspiration biopsy may be employed by some clinicians, this less-invasive means of sampling is inadequate, and a requisite core needle or incisional biopsy must be per-

formed. As the saying goes, “Tissue is the issue” in NHL, so even the excision of an entire lymph node is warranted as part of the diagnostic process in many cases.

In addition to confirming the diagnosis of NHL, a pathologist’s examination of the samples collected via biopsy may reveal the specific type of NHL that has developed in a particular patient. However, in most cases, further laboratory tests are necessary to distinguish the type of lymphoma present. This additional battery of laboratory tests may include immunohistochemistry, flow cytometry, cytogenetics, or advanced molecular genetic studies, such as fluorescent in situ hybridization or polymerase chain reaction. Likewise, blood tests, such as a complete blood count or an assay for lactate dehydrogenase, can help determine how advanced or fast growing a case of NHL may be.²

The results of these biopsies and/



Table 1. Ann Arbor Staging Criteria for NHL (The presence of either criterion in the right column determines disease stage.)²

Stage	Criteria
Stage I	The lymphoma is in a lymph node or nodes in only one region, such as the neck, groin, or underarm.
	The cancer is found in only one area of a single organ outside of the lymph system (IE).
Stage II	The lymphoma is in two or more groups of lymph nodes on the same side of (above or below) the diaphragm.
	The lymphoma extends from a single group of lymph nodes into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm.
Stage III	The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
	The cancer may also have spread into an area or organ next to the lymph nodes (IIIE), into the spleen (IIIS), or both (IIISE).
Stage IV	The lymphoma has spread outside of the lymph system into an organ that is not right next to an involved node.
	The lymphoma has spread to the bone marrow, liver, brain or spinal cord, or the pleura.

or laboratory tests are also employed in staging a patient's NHL. In addition, imaging studies and other types of less-invasive biopsies, such as bone marrow aspiration, lumbar puncture, and pleural or peritoneal sampling, may be used to stage the disease. In terms of imaging, computed tomography (CT) and positron emission tomography (PET) are typically used in tandem, as CT scans reveal the magnitude of NHL involvement, while PET scans offer information about disease activity. Using this information, clinicians most commonly stage NHL according to the Ann Arbor Staging System, which assigns the disease a stage designated by the Roman numerals I through IV.² In general, according to the Ann Arbor Staging System, stage I is characterized by the involvement of one lymph node, stage II is characterized by involvement of multiple lymph nodes on one side of the body, stage III disease is indicated when multiple lymph nodes are involved on both sides of the body, and stage IV is indicated by distal organ involvement.² For further clarification of the Ann Arbor Staging System, please see Table 1.²

As suffixes accompanying the Roman numeral stage, lymphomas that affect an extranodal organ are assigned an *E*, while those affecting the spleen have an *S* added.² Furthermore, each stage is assigned an *A* or *B*, with *B* indicating advanced disease as evidenced by one or more of the following symptoms:²

- Unexplained weight loss (more than 10% of weight)
- Soaking night sweats
- Unexplained fever of at least 101.5 °F

If none of these B symptoms exists, the letter *A* is added to the stage.²

While the Ann Arbor Staging System may be applied to indolent forms of lymphoma, such as small lymphocytic lymphoma/chronic lymphocytic

leukemia confined to the lymph nodes, the Rai system is often used when the disease affects the blood or bone marrow.²

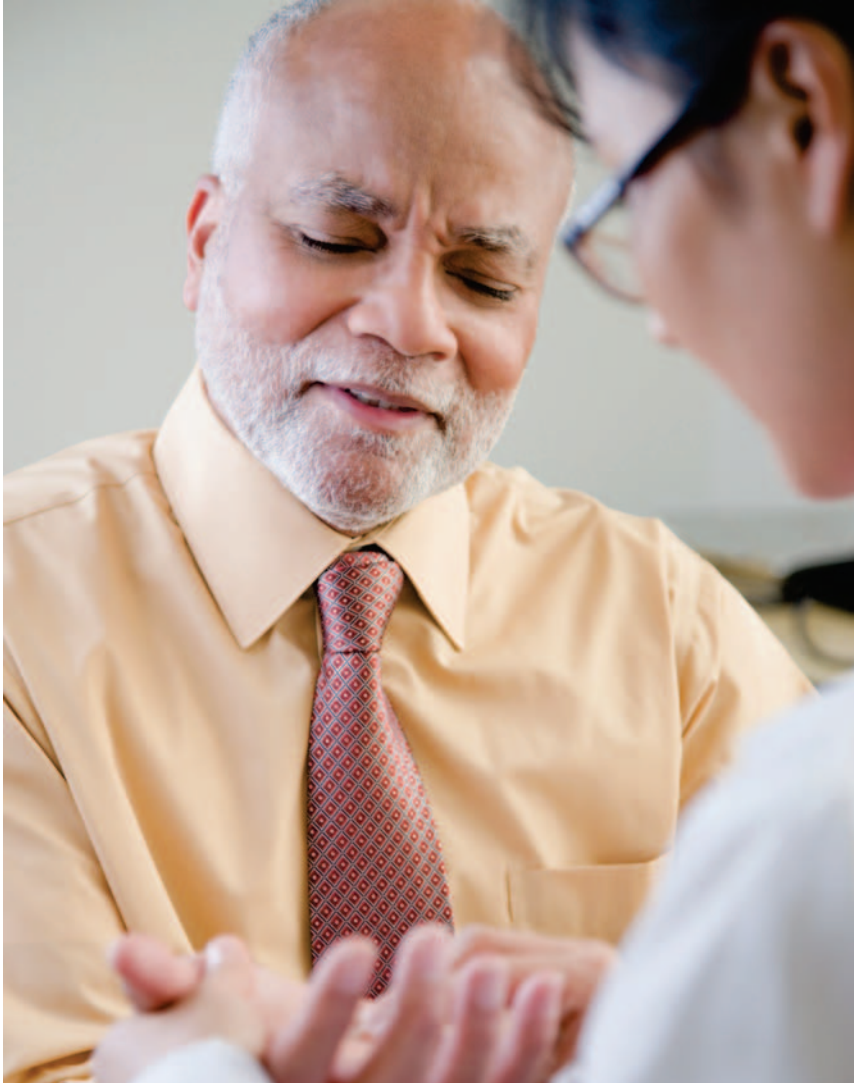
In addition to the stage of NHL, several other factors are considered to predict a patient's prognosis. The score determined by the International Prognostic Index (IPI) for fast-growing lymphomas may be used to assign a patient to one of the following four risk groups: low (zero or one poor prognostic factor), low intermediate (two poor prognostic factors), high intermediate (three poor prognostic factors), or high (four or five poor prognostic factors) (see Table 2).² Demonstrating the IPI's worth in determining prognosis, approximately 75% of people in the lowest risk group live longer than five years, whereas only approximately 30% of people in the highest group live at least five years.² Overall, the five-year relative survival rate for patients with NHL is 67%, and 10-year relative survival is 57%.²

TREATMENT CONSIDERATIONS

In general, chemotherapy is the mainstay of treatment for NHL. While surgery plays virtually no role in disease management, lymphomas are very sensitive to chemotherapy and radiation, and a complete remission is possible in approximately half of cases with these treatment modalities. The universally accepted R-CHOP regimen (rituximab plus cyclophosphamide,

Table 2. The International Prognostic Index²

Good Prognostic Factors	Poor Prognostic Factors
Age ≤ 60 years	Age > 60 years
Stage I or II	Stage III or IV
No lymphoma outside of lymph nodes, or lymphoma in only one area outside of lymph nodes	Lymphoma in more than one organ of the body outside of the lymph nodes
Performance status: able to function normally	Performance status: requires significant assistance with daily activities
Normal serum lactate dehydrogenase	Elevated serum lactate dehydrogenase



hydroxydaunorubicin, Oncovin [vincristine], and prednisone or prednisolone) is administered as first-line therapy in most cases, with disease stage determining the number of cycles. Unlike in other cancers, staging does not necessarily dictate the types of agents employed in the course of treatment, but rather the duration of therapy. For example, whereas patients with various stages of NHL may all receive the R-CHOP regimen, those with stage I and II disease typically receive three cycles, while those with stage III and IV disease typically receive six cycles. In the event of a relapse, clinicians will often attempt to achieve remission with a different chemotherapy regimen than the first-line treatment, after which autologous stem cell transplant is the standard of care.

Rather than the stage, the particular

type of lymphoma identified in a patient drives the course of therapeutic selection. For NHL, rituximab is a key component of therapy because this monoclonal antibody attacks CD20 on B cells. In contrast, the cancer cells in Hodgkin lymphoma do not express CD20, and therefore, do not respond to immunotherapy with rituximab. As such, in those patients with Hodgkin lymphoma, cytotoxic chemotherapy without concomitant biologics is the most commonly accepted course of treatment. Namely, the ABVD regimen (Adriamycin [hydroxydaunorubicin], bleomycin, vinblastine, and dacarbazine) every two weeks is the standard of therapy in Hodgkin lymphoma, with an alternate chemotherapy regimen administered in the event of recurrence. Follicular lymphoma also warrants a different

treatment regimen than B-cell NHL, with a shift toward bendamustine and rituximab instead of R-CHOP in recent years. In treating this indolent form of NHL, maintenance therapy with rituximab every two months over the course of two years has become the standard of care to prevent recurrence. In addition, radioimmunotherapy with tositumomab has been shown to have tripled the progression-free survival for standards of care in relapsing follicular NHL.

Similar to the limited role that disease stage plays in treatment selection for NHL, performance status is of minimal concern when planning a course of therapy. In general, clinicians are more lenient with performance status dictating treatment in NHL than they are with solid cancers. As such, most patients with NHL receive treatment even when their performance status is poor because it is likely the lymphoma itself is making the patient feel poor. Rather than altering the course of treatment, a patient's performance status and age may affect the supportive care agents administered in conjunction with therapy. For example, pegfilgrastim may be administered as supportive care in older patients with NHL to reduce the risk of infection accompanying standard treatment.

FUTURE DIRECTIONS IN MANAGED CARE

The treatment landscape in NHL has evolved significantly over the past decade, most notably with the advent of targeted biologics and radioimmunotherapy. And while rituximab has gained widespread acceptance and utilization as a standard of care in all lines of therapy,

radioimmunotherapy agents, such as tositumomab, remain underused. Beyond these recent advancements, researchers are investigating new indications for existing therapies and novel agents for the treatment of NHL. Specifically, gemcitabine, an agent used in the treatment of solid cancers, and multiple myeloma therapies, such as lenalidomide, are being evaluated for their effectiveness in the treatment of lymphomas.

Among the most promising novel agents studied for the treatment of lymphoma is brentuximab vedotin: an antibody-drug conjugate granted accelerated approval in August 2011 for the treatment of Hodgkin lymphoma and anaplastic large-cell NHL.⁵ Unlike rituximab, which targets CD20, brentuximab vedotin targets the CD30 receptor expressed on cells from patients with Hodgkin lymphoma as well as those from patients with B-cell NHL. In the Hodgkin lymphoma trial, the objective response rate of brentuximab vedotin as monotherapy, as determined by an independent review facility, was 73% (95% CI; 65%, 83%) with a median duration of 6.7 months (95% CI; 4, 14.8).⁵ The complete remission rate was 32% (95% CI; 23.3%, 42.3%) with a median duration of 20.5 months (95% CI; 12, not estimable).⁵ The partial remission rate was 40% (95% CI; 31.5%, 49.4%) with a median duration of 3.5 months (95% CI; 2.2, 4.1).⁵ In anaplastic large-cell NHL, the objective response rate was 86% (95% CI; 77%, 95%) with a median duration of 12.6 months (95% CI; 5.7).⁵ The complete remission rate was 57% (95% CI; 44%, 70%) with a median duration of 13.2 months (95% CI; 10.8).⁵ The partial remission rate was 29% (95% CI; 18%, 41%) with a

median duration of 2.1 months (95% CI; 1.3, 5.7).⁵

Thus far, coverage issues have been minimal in the management of NHL, as the most widely accepted therapeutic regimen is well received by payors and treatment has yielded positive success rates overall. The biology of the disease and the effectiveness of current therapies provide managed care stakeholders with the kind of results that minimize resistance on the payor side, making lymphoma a cancer in which clinicians encounter few administrative barriers. Still, radioimmunotherapy remains underused despite demonstrating great promise in treatment, as it is often not covered and clinicians face hurdles in administration. As more treatment

modalities such as this become available, plans should remain current with emerging data and open to modifying coverage policies to efficiently combat this relatively manageable disease.

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