Intermediate- and High-Grade Non-Hodgkin's Lymphomas

April 01, 2005
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The non-Hodgkin's lymphomas (NHLs) are a collection of lymphoid malignancies with a diverse pathology and natural history. This diversity is illustrated by the different histologic subtypes and classifications of NHL that have appeared over the years.

Introduction

The non-Hodgkin's lymphomas (NHLs) are a collection of lymphoid malignancies with a diverse pathology and natural history. This diversity is illustrated by the different histologic subtypes and classifications of NHL that have appeared over the years. With the rapid progress in our understanding of the biology of lymphomas, new systems of classification have better described this group of diseases. Although the number of classification systems has caused some confusion, in the mid-1970s, the National Cancer Institute (NCI) initiated the NHL pathologic classification project with the aim of standardizing classifications through a Working Formulation (Table 1). This formulation is based on the largest single cohort of patients reported to date and is the framework for this chapter [1,2].

Table 1. A Working Formulation for Non-Hodgkin's Lymphomas (NHL) Classifiable non-Hodgkin's lymphomas

<table>
<thead>
<tr>
<th>Low-grade</th>
<th>Unaccounted-for non-Hodgkin's lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small lymphocytic (CLL)</td>
<td>Mucosa-associated lymphomas</td>
</tr>
<tr>
<td>Follicular, predominantly small-cleaved cell</td>
<td>CD5–, CD10–</td>
</tr>
<tr>
<td>Follicular mixed, small-cleaved and large-cell</td>
<td></td>
</tr>
<tr>
<td>Intermediate-grade</td>
<td></td>
</tr>
<tr>
<td>Follicular, predominantly large-cell</td>
<td>Mantle-cell lymphoma</td>
</tr>
<tr>
<td>Diffuse small-cleaved cell</td>
<td>CD5+, CD23–, t11;14 PRAD1</td>
</tr>
<tr>
<td>Diffuse mixed small- and large-cell epithelioid component</td>
<td>Lennert's lymphoma</td>
</tr>
<tr>
<td>Diffuse large-cell cleaved, T-cell variants, non-cleaved</td>
<td>T-cell+</td>
</tr>
<tr>
<td></td>
<td>Transformed from low-grade NHL</td>
</tr>
</tbody>
</table>
Intermediate- and High-Grade Non-Hodgkin's Lymphomas

Published on Psychiatric Times
(http://www.psychiatrictimes.com)

High-grade
- Large-cell, immunoblastic
- Plasmacytoid, clear-cell, polymorphous, epithelioid
- Small non-cleaved cell
- Burkitt's
- Follicular areas

Miscellaneous
- Composite
- Mycosis fungoides/Szary syndrome
- Histiocytic
- Unclassifiable

Anaplastic large-cell T-cell (rare B), Ki-1(CD30)+, t2;5

Other T-cell NHL
- HTLV-1 lymphoma
- T-cell CLL
- Angioimmunoblastic lymphadenopathy dysproteinemia

Angiocentric-type
- Polymorphic reticulosis
- Lymphomatoid granulomatosis

The Working Formulation is useful as a source of prognostic information and a tool for treatment planning. However, several of its limitations deserve mention. First, nearly 10% of the lymphomas encountered in practice elude precise classification, particularly lymphomas presenting primarily in extranodal tissues where there is no lymph-node architecture. In these cases, clinical experience and certain tests can help to predict the natural history of the disease. Second, within the broad histologic categories of low-, intermediate-, and high-grade lymphomas, there can be a wide spectrum of biologic behavior, as illustrated by the survival curves from the NCI project (Figure 1). Third, histopathologic classification alone is inadequate in some cases, as sometimes there is less-than-ideal interobserver agreement [3]. Immunophenotyping, cytogenetics, and specific oncogene studies have been found to be important factors in diagnosing clinically unique subtypes of NHL. Lymphomas not accounted for by the Working Formulation are listed in Table 1, with their unique immunophenotype or cytogenetic abnormalities next to the histologic subtype with which they are typically associated.

Figure 1. Actuarial survival curves for the 10 subtypes of the formulation shown individually (upper panel) and in the three prognostic categories (lower panel). Curves are discontinued when less than five patients are at risk. Adapted, with permission, from Cancer 1982 [1].

Indeed, the limitations of the Working Formulation have prompted further discussion, and another classification system has now been introduced (Table 2) [4]. This chapter, however, will follow the categorization of the Working Formulation.

Table 2. Classification of Lymphoid Neoplasms

<table>
<thead>
<tr>
<th>B-cell Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precursor B-cell neoplasms</strong></td>
</tr>
<tr>
<td>Precursor B-lymphoblastic leukemia/lymphoma</td>
</tr>
<tr>
<td><strong>Peripheral B-cell neoplasms</strong></td>
</tr>
<tr>
<td>B-cell chronic lymphocytic leukemia/prolymphocytic leukemia/small lymphocytic lymphoma</td>
</tr>
<tr>
<td>Lymphoplasmacytoid lymphoma/immunocytoma</td>
</tr>
<tr>
<td>Mantle-cell lymphoma</td>
</tr>
<tr>
<td>Follicle center lymphoma, follicular</td>
</tr>
</tbody>
</table>

- Provisional grades: 1 (small-cell), 2 (mixed), 3 (large-cell)
- Provisional subtype: diffuse, predominantly small-cell

Marginal zone B-cell lymphoma
Intermediate- and High-Grade Non-Hodgkin's Lymphomas

- Extranodal (MALT-type ± monocytoid B cells)
- Provisional subtype: Nodal (monocytoid B cells)

Provisional entity: Splenic marginal zone lymphoma
  (± villous lymphocytes)
- Hairy-cell leukemia
- Plasmacytoma/plasma-cell leukemia
- Diffuse large B-cell lymphoma subtype: Primary mediastinal B-cell lymphoma
- Burkitt's lymphoma
- Provisional entity: High-grade B-cell lymphoma, Burkitt-like

T-Cell and Putative NK-cell Neoplasms

**Precursor T-cell neoplasm**
- Precursor T-lymphoblastic lymphoma/leukemia

**Peripheral T-cell and NK-cell neoplasms**
- T-cell chronic lymphocytic leukemia/prolymphocytic leukemia
- Large granular lymphocyte leukemia
  - T-cell type
  - NK-cell type

- Mycosis fungoides/Szary syndrome
- Peripheral T-cell lymphomas, unspecified
- Angioimmunoblastic T-cell lymphoma
- Angiocentric lymphoma
- Intestinal T-cell lymphoma (± enteropathy associated)
- Adult T-cell leukemia/lymphoma
- Anaplastic large-cell lymphoma, CD30+, T and null-cell type
- Provisional entity: Anaplastic large-cell lymphoma, Hodgkin's-like

Hodgkin's Disease
- Lymphocyte predominance
- Nodular sclerosis
- Mixed cellularity
- Lymphocyte depletion
- Provisional entity: Lymphocyte-rich classic Hodgkin’s disease

**Epidemiology and Etiology**

At present, there is an emerging unexplainable epidemic of NHL [5]. In the United States, the incidence has increased from 6.9 per 100,000 population in 1947 to 1950 to 17.4 per 100,000 population in 1984 to 1988. Changes in exposure to described risk factors (Table 3) [5-14] do not explain this increase, much of which is largely caused by a rise in intermediate-grade lymphomas among the elderly. Another unexplained phenomenon is the slight but consistent predominance of NHL incidence in men (male:female ratio 1.5 to 1.25:1).

**Table 3. Epidemiologic Risk Factors for Non-Hodgkin's Lymphoma (NHL)**

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Hereditary immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia-telangiectasia</td>
<td>Bruton-type agammaglobulinemia</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>Duncan's syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Intermediate- and high-grade tumors comprise nearly 55% of NHLs, with a proportionately higher number of high-grade tumors in children and young adults [1]. Ninety percent of childhood NHLs are Burkitt’s NHL, T-cell acute lymphoblastic lymphoma (T-ALL), or diffuse large-cell lymphoma with a Ki-1 immunophenotype.

Despite the variation with age in the incidence of certain types of NHL, the biology, including underlying molecular defects, appears relatively uniform within a histologic subtype. There is no single defect that alone causes a lymphoma. The etiology and pathogenesis of intermediate- and high-grade lymphomas are considered parts of a multistep process in which the malignant phenotype develops gradually. Hereditary and environmental factors contribute to this process. Hereditary factors, childhood lymphomas, and high-grade tumors are closely associated. Some of these associations and others, are presented in Table 3 and referenced.

Three factors appear common to the etiology of lymphomas. The first is that certain patients may be predisposed to develop a type of lymphoma because of a generalized or, perhaps, specific immune defect. This “host” defect frequently includes autoimmune diseases. The second factor is the occurrence of a specific infection that is difficult to eradicate and that may alter normal lymphoid tissues. The third factor is that a single specific mutation or a number of specific mutations or chromosome translocations can alter suppressor genes or oncogenes, respectively, and result in a lymphoma. With any specific lymphoma, any or all of these factors may be at work.

A number of specific diseases illustrate how immune factors contribute to lymphomagenesis. Duncan’s syndrome, or X-linked lymphoproliferative syndrome, is a particularly interesting example [15]. Males with this syndrome are unable to mount an appropriate immunologic response to an Epstein-Barr virus (EBV) infection. They develop a fatal lymphoproliferative syndrome when first infected. The precise immune defect in these patients is not known.

Posttransplant lymphoproliferative syndrome is strikingly similar [12]. Immunosuppression following solid-organ transplantation can cause an EBV infection-related polyclonal lymphoproliferative disease that can develop into a typical NHL if immunosuppression is not stopped. The primary central nervous system (CNS) lymphomas associated with the human immunodeficiency virus (HIV) may develop in a similar fashion following EBV infection [6]. These examples show how an immune
defect coupled with an infection can lead to a lymphoma. Viruses such as EBV, human T-cell leukemia virus-1 (HTLV-1), and HIV are not the only infectious agents that can interact to cause lymphomas. *Helicobacter pylori* is a bacterium that has been found to cause gastric ulcers as well as gastric lymphomas [9]. The pathogenesis is still being determined, but it is possible to cure some gastric lymphomas with the triple antibiotic regimen used to eradicate *H pylori*. Thus, removing an infectious agent can possibly lead to curing a lymphoma. Similarly, in posttransplant lymphoproliferative disease, stopping the immunosuppression early in the process can prevent the development of a lymphoma. In both posttransplant lymphoproliferative disease and *H pylori* associated gastric lymphoma, beyond a certain point, reversing the offending agent does not lead to the resolution of the lymphoma. This suggests that another step occurs, conferring a nonreversible malignant phenotype.

In some cases, this last step may involve the mutation of a suppressor gene causing loss of tumor suppression, or a chromosome translocation, causing the abnormal expression of an oncogene. Both of these processes may in turn cause the loss of normal cellular responses. Tumor-suppressor genes have a number of functions, but many of them seem to suppress tumors by regulating the cell cycle and, in turn, proliferation. A good example of this is the transformation of typical low-grade follicular NHL into intermediate NHL through the development of a *p53* mutation [16]. Table 4 presents the known translocations and their oncogenes involved in lymphomagenesis [17].

Table 4. Translocations and Oncogenes Involved in Lymphomagenesis

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Chromosome</th>
<th>Affected type translocation</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt's NHL</td>
<td>t(8;14)</td>
<td>c-(\text{MYC}) (8q24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(8;22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCL-NHL</td>
<td>t(3;14)</td>
<td>BCL-6 (3q27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(3;4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantle NHL</td>
<td>t(11;14)</td>
<td>BCL-1 (11q23)</td>
<td></td>
</tr>
<tr>
<td>Transformed NHL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL-B and -T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-NHL</td>
<td>Inv 14</td>
<td>TCR-Ca (14q11)</td>
<td></td>
</tr>
<tr>
<td>Ki-1 anaplastic</td>
<td>t(2;5)</td>
<td>NPM (5q35/ALK (2p23)</td>
<td></td>
</tr>
</tbody>
</table>

Perhaps the single best example of the modern paradigm of lymphomagenesis is the pathogenesis of African or endemic Burkitt's NHL [7]. Endemic Burkitt's NHL is found in areas of Africa with a high incidence of malaria. Malaria may cause a defect in the immune system of children residing in these areas, which results in their inability to resolve EBV infections successfully. Following EBV infection, which is serologically documented in more than 90% of cases of endemic Burkitt's lymphoma, the lymphoma finally develops when a chromosome translocation brings the *c-myc* oncogene on chromosome 8 into the proximity of an immunoglobulin gene on either chromosome 2, 14, or 22 and its regulatory sequences. The *c-myc* oncogene then becomes overexpressed through its abnormal transcription mediated by the immunoglobulin gene-regulatory sequences, causing cellular proliferation and Burkitt's lymphoma.

Nonendemic Burkitt's NHL has a different presentation from that of endemic Burkitt's NHL; it is less frequently associated with EBV, and it has a different translocation breakpoint between the *c-myc* and immunoglobulin genes. All these factors suggest a different pathogenesis for nonendemic Burkitt's NHL [18]. The mechanism that causes one step to lead to the next still remains unknown. We are just beginning to scratch the surface of this complex problem, but as genes and their functions become better understood, it is likely that, in the future, lymphomas will be diagnosed and treated based on their specific genetic abnormalities.
Clinical Features and Diagnosis

Sites Of Presentation
The clinical manifestations of intermediate- and high-grade NHLs are diverse and depend on the site of disease involvement. These tumors have a rapid growth rate and present as masses that cause symptoms when they infiltrate tissues or obstruct organs. The more aggressive the lymphoma, the more frequently it is localized. Pain within an enlarged lymph node may also be noted if the tumor is rapidly growing.

Lymphomas appear most frequently in sites with the most lymphoid tissue. Thus, the lymphoid and reticuloendothelial system, which includes the lymph nodes, spleen, liver, and bone marrow, is most frequently involved, but any extranodal site may also be primarily involved. Certain lymphomas have classic anatomic presentations. However, these features are not invariably present, except perhaps in the cutaneous postthymic T-cell lymphomas, which include mycosis fungoides and Szary syndrome. Endemic Burkitt's NHL frequently presents as a head and neck mass in a child. T-ALL frequently presents with a mediastinal mass in younger patients [19].

Anaplastic large-cell lymphoma with positive Ki-1 staining (CD30+) in younger patients is another variant with frequent cutaneous presentation and a predilection for extranodal tissue [20]. A clinically distinct primary mediastinal B-cell diffuse large-cell lymphoma presents in young women [21]. The gastrointestinal tract is often involved in certain types of lymphoma. This is the case with many mucosa-associated lymphoid tissue (MALT) lymphomas, 15% of mantle-cell lymphomas, 10% of intermediate-grade lymphomas of Waldeyer's ring and sinuses, and rare lymphomas (enteropathy-associated T-cell NHL, immunoproliferative small-intestinal disease, and Mediterranean lymphoma) [22]. Certain predisposing conditions will also have a classic extranodal tissue presentation. Patients with Hashimoto's thyroiditis are predisposed to primary thyroid lymphomas, patients with Sjogren's syndrome to primary salivary and lacrimal gland NHL, and patients with celiac disease to enteropathy-associated T-cell NHL.

Involvement of “sanctuary” sites, which include the CNS and testicles, is more frequently associated with Burkitt's NHL and non-Burkitt's small-cell NHL, T-ALL, primary testicular diffuse large-cell lymphoma [23], HIV-associated aggressive B-cell lymphoma, and HTLV-1 associated lymphoma.

Systemic Features
As with Hodgkin's disease, NHL also presents with systemic B symptoms, including fever, which may or may not have the Pel-Ebstein relapsing pattern; drenching night sweats; and more than 10% weight loss. Generalized pruritus may also be present. Paraneoplastic syndromes may also develop with these types of lymphomas. Nonparathyroid hormone induced hypercalcemia occurs in approximately 10% of patients [24]. Hypercalcemia also is frequently associated with HTLV-1 T-cell lymphomas. Subacute motor neuropathy and polymyositis may also be linked with NHL [25].

Diagnosis
A diagnosis of NHL, as well as suspected relapses, should be made based on the pathologic examination of a lymph node whenever possible. The accuracy of fine-needle aspiration (FNA) is variable. In one trial, lymphomas were diagnosed using FNA in 86% of cases and were accurately categorized into low, intermediate, or high grade in 68% of cases [26]. In some instances, it may be necessary to establish clonality to confirm malignancy. Clonality is established when one can be proved that all cells in a lymphoma were derived from a single cell. In B-cell NHL, monotypic immunohistochemical staining for kappa or lambda light chain is often all that is needed to confirm clonality. In some cases, one may need to establish clonality by performing studies on either T-cell receptor rearrangement or J-H segment rearrangements of the B-cell immunoglobulin gene. Gene rearrangement studies are diagnostic and reliable in more than 96% of these cases [27]. Occasionally, a specific diagnosis can be made by cytogenetic analysis. Some of these specific chromosomal translocation fusion genes are amenable to polymerase chain reaction assays, which can then be used in studies of minimal residual disease (Table 4) [17].

Staging and Treatment
Staging allows clinicians to prognosticate and then treat appropriately. The staging of intermediate- and high-grade non-Hodgkin's lymphomas has become an area of intense research. For some time, NHL was staged anatomically, like Hodgkin's disease. It has become clear, however, that unlike Hodgkin's disease, NHL does not spread anatomically to contiguous nodal regions and, therefore, cannot be reliably staged solely by anatomic methods.
The treatment of Hodgkin's disease and NHL has formed the modern paradigm of cancer chemotherapy. The basic concepts were first established for infectious diseases and then applied to oncology. Skipper and colleagues, followed by Goldie and Coldman, established the principles of tumor resistance and, in turn, combination chemotherapy and non-cross-resistant chemotherapeutic regimens [28,29]. The curability of advanced cancer ushered in the modern era of oncology. Today, the principal treatment for NHL is combination chemotherapy and radiation therapy. Surgery is used chiefly as a diagnostic tool, with some unique exceptions. Combination chemotherapy with cyclophosphamide (Cytoxan, Neosar), doxorubicin (Adriamycin, Rubex), vincristine (Oncovin), and prednisone—the CHOP regimen—was developed at M.D. Anderson Cancer Center and introduced in the 1970s. Since then, a number of second- and third-generation regimens and combinations of non-cross-resistant regimens for intermediate- and high-grade NHLs have been developed. The benefit of these newer regimens is now in question, but some issues are not yet clearly resolved. Current trials of chemotherapy for NHL may hold the answers.

Intermediate Grade NHL

Staging

A number of staging systems for intermediate-grade NHL have been developed based on retrospective evaluation of clinical, laboratory, radiologic, and pathologic data for patient cohorts. Table 5 [30-33] lists the individual prognostic factors studied to date that have been related to outcome in intermediate-grade NHL [30,34,35]. These factors can be grouped into categories that reflect different aspects of the disease: host factors, tumor burden, and tumor biology as they relate to pathogenicity and drug resistance. Performance status, lactate dehydrogenase (LDH) level, and extent of tumor have been validated prospectively as reliable prognostic factors [36].

Table 5. Individual Prognostic Factors in Intermediate-Grade NHL

<table>
<thead>
<tr>
<th>Prognostic Factors [30-33]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Host factors</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>&quot;B&quot; symptoms</td>
</tr>
<tr>
<td>Performance status</td>
</tr>
<tr>
<td><strong>Tumor burden</strong></td>
</tr>
<tr>
<td>Ann Arbor stage</td>
</tr>
<tr>
<td>Number of extranodal sites</td>
</tr>
<tr>
<td>Bulky sites</td>
</tr>
<tr>
<td>Serum LDH level</td>
</tr>
<tr>
<td>Serum beta-2-microglobulin</td>
</tr>
<tr>
<td><strong>Tumor biology</strong></td>
</tr>
<tr>
<td>Pathogenicity</td>
</tr>
<tr>
<td>B- vs T-cell</td>
</tr>
<tr>
<td>S-phase percent</td>
</tr>
<tr>
<td>Ki-67 expression</td>
</tr>
<tr>
<td>CD-44 expression</td>
</tr>
<tr>
<td>HLA-DR expression</td>
</tr>
<tr>
<td>IL-10 serum concentration</td>
</tr>
<tr>
<td>Soluble IL-2 receptor levels in serum</td>
</tr>
<tr>
<td>Cytogenetics 7-, 17P-</td>
</tr>
<tr>
<td>BCL-2 expression</td>
</tr>
<tr>
<td>BCL-6 expression</td>
</tr>
<tr>
<td>Drug resistance</td>
</tr>
<tr>
<td>Response after three cycles of chemotherapy</td>
</tr>
<tr>
<td>MDR-1 gene expression</td>
</tr>
</tbody>
</table>

Many of the other factors are still under investigation, and testing for some of the serologic parameters is not routinely performed. In the future, however, some of these factors may replace or complement existing ones, because even our best current prognostic models have less than
desirable positive and negative predictive values. At M.D. Anderson, disease is staged according to the “tumor score” system, which is compared in Table 6 with the other frequently used system, the International Index [34,35].

Table 6. Comparison of Two Staging Systems for Intermediate- and High-Grade Non-Hodgkin’s Lymphomas (NHL): International Index vs Tumor Score System

<table>
<thead>
<tr>
<th>Factor</th>
<th>International index</th>
<th>M.D. Anderson tumor score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Yes = 1 point</td>
<td>N/A</td>
</tr>
<tr>
<td>Ann Arbor stage: 3 or higher</td>
<td>Yes = 1 point</td>
<td>N/A</td>
</tr>
<tr>
<td>2 or more extranodal sites</td>
<td>Yes = 1 point</td>
<td>N/A</td>
</tr>
<tr>
<td>2 or higher Zubrod performance status</td>
<td>Yes = 1 point</td>
<td>N/A</td>
</tr>
<tr>
<td>High LDH &gt; 250 IU at MDA</td>
<td>Yes = 1 point</td>
<td>Not included</td>
</tr>
<tr>
<td>Beta-2-microglobulin &gt; 3.0 at MDA</td>
<td>Not included</td>
<td>Y</td>
</tr>
<tr>
<td>B symptoms</td>
<td>Not included</td>
<td>Y</td>
</tr>
<tr>
<td>Number of sites of bulky (&gt; 7 cm diameter) NHL</td>
<td>Not included</td>
<td>Y</td>
</tr>
<tr>
<td>Total possible points</td>
<td>0 to 5 points</td>
<td>0 to 6 points</td>
</tr>
</tbody>
</table>

The main advantage of the M.D. Anderson tumor score is that it appears to separate more clearly tumors with a good prognosis from tumors with a poor prognosis (Table 7).

Table 7. Comparison of M.D. Anderson Tumor Score vs International Index Score with Regard to Prognosis

<table>
<thead>
<tr>
<th>M.D. Anderson tumor score</th>
<th>CR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 2</td>
<td>91</td>
</tr>
<tr>
<td>3 to 6</td>
<td>46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>International index score</th>
<th>CR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>4 to 5</td>
<td>44</td>
</tr>
</tbody>
</table>

Localized and Good Prognosis Disease

It is possible to treat nonbulky, localized Ann Arbor stage-I NHL with involved-field radiation therapy alone, which yields a 5-year disease-free survival (DFS) rate of 77% with salvage chemotherapy [37]. However, most physicians treat localized intermediate-grade NHL with chemotherapy plus involved-field radiation therapy. Patients with good-risk stages-I and -II disease have achieved a 5-year DFS rate of 84% with 4 cycles of CHOP plus regional radiation therapy [38,39]. With the newer tumor staging systems, all these patients would have low scores and favorable disease, except the elderly and patients with bulky disease, who were shown in these studies to relapse more frequently. These latter patients with high-risk localized disease are now treated as patients with advanced disease at M.D. Anderson Cancer Center.

Localized extranodal NHL in the stomach, thyroid, sinuses, or Waldeyer’s ring, unless the tumor is very small and localized, is best managed with combination chemotherapy and radiation therapy [31,40]. The issue of using prophylactic gastric resection to prevent perforation by chemotherapy in
gastric lymphomas is still not resolved and will depend on the patient’s condition [41]. Primary NHL of the CNS is a rare and not very favorable form of localized NHL, with a mean survival duration of approximately 19 months in patients without HIV [42]. Radiation therapy alone is standard treatment but has achieved disappointing results. The addition of high-dose intravenous methotrexate may improve the mean survival duration but increases the risk of leukoencephalopathy. Finally, testicular lymphoma frequently appears in the CNS or the contralateral testis; its management with prophylactic cranial and testicular irradiation has been debated [23].

**Advanced Disease**

Developed in the late 1960s at M.D. Anderson Cancer Center and tested by the Southwest Oncology Group (SWOG) in the 1970s, CHOP was the first combination chemotherapeutic regimen to demonstrate cures in intermediate-grade NHL. During the 1980s, a number of trials showed improved survival with the newer, more complex second- and third-generation chemotherapeutic regimens. This prompted the SWOG phase-III trial in patients with bulky disease Ann Arbor stage-II or higher who were stratified for age, marrow development, histology, bulky disease sites, and LDH level. This trial compared CHOP with methotrexate, bleomycin (Blenoxane), doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD); prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide (VePesid), cytarabine, bleomycin, vincristine, and methotrexate (ProMACE-CytaBOM); and methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (MACOP-B) [43].

This trial showed that eight cycles of CHOP chemotherapy was capable of inducing a complete response (CR) rate of 44% and an estimated 3-year DFS rate of 41%. The other regimens did not produce statistically better results; instead, they had more fatal and life-threatening toxic effects. One debated conclusion of this trial is that increasing the dose intensity of chemotherapy does not improve results. Another is that CHOP remains the standard of care for advanced intermediate-grade NHL, even though the results are far from ideal. We can now fairly accurately predict which patients have only a 20% chance of surviving for 3 years, and the current problem is how to best treat those poor prognosis patients.

One group of patients who fares poorly is those more than 60 years old. There has been some question as to whether the biology of tumors in the elderly differs somehow from that of tumors in younger age groups. A recent study of prognostic factors in elderly patients who had undergone chemotherapy where dose intensity was maintained found that age did not alter survival [44]. Elderly patients, it appears, are underdosed to avoid increased toxicity, even when they present with good performance status and marrow function. Dose intensity may be important not only in the elderly but in all patients [45,46]. In a related issue, the use of growth factors in NHL may most reasonably be applied to the maintenance of standard dose intensity in the compromised patient, even though no survival benefit has yet been shown [47]. Dose intensity is also maintained by experience with a particular regimen. Removing these confounding variables may reduce the influence of age on treatment response and outcome.

In terms of chemotherapy, it would then seem that less is bad, but more is not necessarily better. Again, the issue of dose intensity is not so simple. There are a number of biologic variables that may confound the data and obscure cases in which more is better or in which nothing works. Some progress is being made in this regard. There is some evidence that second- or third-generation combination chemotherapeutic regimens improve CR and DFS rates in young patients with primary mediastinal B-cell diffuse large-cell lymphoma and Ki-1 anaplastic T-cell NHL [48,49].

At M.D. Anderson, the alternating triple therapy (ATT) regimen, which consists of alternating non-cross-resistant regimens—ASHAP (doxorubicin, methylprednisolone, high-dose cytarabine, cisplatin), MBACOS (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, solumedrol), MINE (mesna, ifosfamide, mitoxantrone, and etoposide)— has shown a significant benefit in the highest-risk patients, although further follow-up is needed [50]. Greater dose intensity is also being used to treat other subgroups of patients [51]. On the other hand, some lymphomas may be inherently resistant to current chemotherapy. T-cell variants of diffuse large-cell NHL have poorer response rates than B-cell types [52,53]. The diffuse mantle-cell NHL is another subtype with poor response [54].

Patients who do not achieve a CR by the end of the first three cycles of the CHOP regimen also are at high risk [55]. One approach in these patients has been to switch therapy to a non-cross-resistant regimen and to include late dose intensification, which has shown some improvement over historic controls [56]. A recent investigation attempted to improve responses in these slowly responding patients by autologous bone marrow transplantation (ABMT), but no improvement in overall survival or DFS was shown at 3 years [57]. Further follow-up is needed, but at this stage, ABMT does not
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Published on Psychiatric Times
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appear to be the answer.

In general, approximately 45% of patients with the worst prognosis will obtain a CR, but many will then relapse; only about 25% will survive long term. A major area of focus has been consolidation treatments that can prevent relapse. Radiation therapy for sites of bulky disease seems to improve results in certain subsets of patients but not in others [58]. ABMT is currently being compared with sequential conventional-dose combination chemotherapy in these patients; initial reports of ABMT seemed favorable [59], but a recent randomized trial of 464 patients did not show a benefit for ABMT overall [60]. Again, further follow-up is needed, and new approaches seem warranted.

**Relapse and Primary Refractory Disease**

In some patients, confirming the presence of persistent disease or early relapse can be difficult. Computed tomography scanning will readily identify residual masses in up to 40% of patients with bulky abdominal disease. Few of these patients, 5% in one review, actually had residual disease on laparotomy [61]. FNA biopsy may be inaccurate because of sampling errors, and gallium scans are operator-dependent [62]. These factors pose problems when interpreting results and managing some patients.

At present, there is no accepted standard of therapy for patients with primary refractory disease and relapsed disease. Current research has focused in two directions. The first approach has been high-dose chemotherapy with autologous stem-cell rescue to exploit the demonstrated dose-response curve of various chemotherapeutic agents. The second approach has been dose-intensive non-cross-resistant standard chemotherapeutic regimens to circumvent drug resistance. In the next few years, other avenues are likely to be explored.

ABMT is limited to patients younger than 60 years of age and has yielded 3-year DFS rates of 30% to 40% in patients who had a relapse after achieving a CR with conventional chemotherapy. Patients who had primary refractory disease and patients who achieved a partial response to conventional chemotherapy had 3-year DFS rates of 0% and 14%, respectively [63].

Nearly 10% of patients who relapse will be able to achieve long-term DFS with current salvage combination chemotherapy regimens. A variety of reasonably successful salvage regimens have been developed, including MIME (mesna, ifosfamide, methotrexate, and etoposide) [64], DHAP (dexamethasone, high-dose cytarabine, and cisplatin) [65], and ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) [66], which produce CR rates of 20% to 30%, and sequential MINE (mesna, ifosfamide, mitoxantrone, and etoposide)-ESHAP [66], which produces a CR rate of 43%. These CR rates are seen primarily in patients with a better prognosis who previously achieved a CR with standard chemotherapy and relapsed with a low-volume of disease more than 6 months after stopping treatment. A recent phase-III trial compared ABMT in a group of patients responding to salvage chemotherapy with another group who was continued on salvage chemotherapy. Although the results are preliminary, there appears to be no difference between the groups in the rate of DFS [68].

Various new approaches include continuous-infusion chemotherapy [69], the use of P-glycoprotein-blocking agents along with chemotherapy [70] and other biologic agents [71]. Allogeneic BMT has also been explored in a select subset of patients, with variable results [72].

**High-Grade Tumors**

Immunoblastic large-cell NHL is clinically indistinguishable from intermediate-grade NHL and is treated the same way. Lymphoblastic NHL, Burkitt's NHL, and non-Burkitt's NHL, on the other hand, behave more like ALL. These tumors double in size quicker than any other tumor, and they are rapidly fatal. The tumor lysis syndrome (see the chapter on Oncologic Emergencies) is commonly seen with the initiation of or even prior to therapy. Like ALL, these lymphomas have a predilection for the CNS. Prognostic factors are the same as those for ALL: age, LDH level, and CNS or bone-marrow involvement.

For adult lymphoblastic lymphoma, the treatment has been similar to that for adult ALL, which is based on vincristine, doxorubicin, and high-dose glucocorticoids [19,73]. CR rates have been as high as 95%, but DFS rates average 35% to 56%. These regimens are complex and protracted, with long maintenance phases, radiation therapy for the mediastinum, and CNS prophylaxis. (See the chapter on Acute Lymphoblastic Leukemia).

The treatment of adults with Burkitt's and non-Burkitt's NHLs is based on high-dose alkylating agents, usually cyclophosphamide, plus other cell cycle phase-specific agents [74,75]. In patients with a good prognosis, the overall CR rate is nearly 77% to 85%, and the 5-year DFS rate is about 60%. Favorable patients can also be treated with more standard chemotherapeutic regimens for
lymphoma, such as ProMACE-CytaBOM, with good results [76]. Patients with a poor prognosis have a decidedly worse outcome, with a DFS rate of 20% to 30%. The role of bone marrow transplantation in these patients has not been established, but this therapy is often attempted in patients whose disease relapses.

Special Cases

Human Immunodeficiency Virus: Patients with HIV are at particularly high risk of developing intermediate- and high-grade NHL. Nearly 10% of patients with HIV will die as a result of a lymphoma. Poor prognostic factors for these patients have been a poor performance status, prior AIDS (acquired immunodeficiency syndrome)-defining illness, a low CD4 count, marrow involvement, and an elevated LDH level [77,78]. Treatment of these patients is difficult and quickly evolving. For intermediate-grade NHL, full-dose chemotherapy for less-debilitated patients can be tolerated and has achieved a CR rate of 77% and a 2-year survival rate of 34%. More advanced patients have been treated with low-dose M-BACOD. When this treatment was compared with regular-dose M-BACOD plus granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]) [79], there was no difference between the two in CR or survival. Neither the role of CNS prophylaxis nor that of antiretroviral treatment has been established in this setting. The management of high-grade NHLs is based on individual factors because many patients cannot tolerate the intensive chemotherapy. Many high-grade lymphomas present as a primary CNS lymphoma in patients with HIV. In this situation, whole-brain radiation with a boost to the tumor is standard therapy and results in a CR rate of 50% and a mean survival duration of 2 to 4 months [42]. Survival is not altered in these cases, but quality of life is improved.

T-cell NHLs are a confusing group of diseases that are largely ignored by the working formulation but more clearly delineated by the new classification. Although some of these diseases have already been discussed (ALL, the Ki-1 [CD30+] anaplastic large-cell lymphoma, and the unspecified peripheral T-cell NHL), several others deserve mention.

Mycosis fungoides and Szary syndrome are clinically distinct types of postthymic (mature) T-cell NHL characterized by cutaneous plaques of CD4+ T-cells progressing to nodal and visceral involvement in the former and by a generalized erythroderma with circulating abnormal lymphocytes progressing to visceral involvement in the latter. Both diseases are generally indolent (behaving like a low-grade NHL), with a mean survival duration of at least 10 years with cutaneous involvement and of only about 2 years when the viscera are involved. Neither is curable with current therapy [80]. Both diseases are amenable to effective palliative therapy. There are numerous treatment options; the choice depends largely on the extent of the disease. In general, early disease confined to the skin is best treated with either topical mechlorethamine hydrochloride, oral psoralens and photopheresis, or whole-skin electron-beam radiation therapy. As the disease progresses, systemic therapy with single-agent chemotherapy, interferon, or retinoids may be attempted. Lastly, some form of combination chemotherapy is often used [81]. A conservative approach is supported by the results of the NCI randomized trial comparing combination chemotherapy plus electron-beam radiation with topical chemotherapy, which did not show a difference in survival despite differences in responses [82].

HTLV-1-associated adult T-cell leukemia/lymphoma (ATLL) is another distinct type of T-cell lymphoma characterized by endemic regions of seropositivity for the virus in southwest Japan and the Caribbean, unique clinical features (including prominent systemic symptoms), frequent cutaneous involvement, hypercalcemia, and poor response to therapy. Several broad clinical stages of ATLL are recognized, from smoldering ATLL (in which a few circulating ATLL cells are present with transient skin lesions), through a chronic stage with lymphocytosis and mild nodal or visceral enlargement, to the acute form with marked lymphocytosis, hepatosplenomegaly, other organ involvement, systemic symptoms, and hypercalcemia. Another stage is characterized by the absence of lymphocytosis but the presence of prominent lymphadenopathy. This stage behaves aggressively, like the acute form [83]. Serum interleukin-2 receptor levels have been useful in separating patients with acute disease from patients with chronic disease and in predicting response to therapy [84]. The 2-year survival rate for the smoldering and chronic forms is 52% to 78% but only about 20% for the acute form [83]. Generally, no treatment is recommended for the smoldering and chronic forms, whereas combination chemotherapy has been attempted for the acute form, without appreciable improvement in survival.

Conclusion

Despite the great strides in our understanding of NHL, there remain many unanswered questions
about its etiology in light of the current epidemic, its pathophysiology as it relates to advances in molecular biology, and its treatment in the case of patients with poor prognosis.

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