Clinical practice guidelines: non-Hodgkin's lymphomas

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BACKGROUND Despite the common clonal origin of the non-Hodgkin's lymphomas (NHLs), their characteristic diversity contributes to the difficulty of defining comprehensive treatment regimens.

OBJECTIVES To review and compare historical and current data that define practice guidelines in the treatment of the NHLs.

DISCUSSION *Early-stage, low-grade NHLs:* Irradiation remains the standard treatment. *Late-stage, low-grade NHLs and advanced-stage indolent lymphomas:* Alkylating agents (eg, chlorambucil, cyclophosphamide) are the standard response, although recent studies suggest maintaining a vigilant, watch-and-wait course anticipatory of intervention. Some new therapies, alone or in combination, offer potential for development (eg, the chemotherapeutic agents fludarabine, 2′-deoxycoformycin, and 2-chlorodeoxyadenosine for low-grade NHLs, and bone marrow transplantation, monoclonal antibodies, and recombinant interferon-alfa for advanced-stage indolent lymphomas). *Intermediate-grade aggressive and high-grade NHLs:* Combination chemotherapy (ie, CHOP) is the historical treatment, plus regional irradiation, with CNS prophylaxis an additional option in high-grade lymphoblastic disease, and bone marrow transplantation an additional option in large-cell immunoblastic and small noncleaved-cell NHLs.

CONCLUSIONS Presently accepted therapies remain the mainstays in treating the NHLs; however, progressive therapeutic regimens, such as watching and waiting for intermediate-level disease progression or employing salvage, high-dose chemotherapeutic regimens, often with bone marrow transplantation, in intermediate- or high-grade disease stages, have yielded measurable successes in significant minorities of patients.

INDEX TERMS: LYMPHOMA, NON-HODGKIN'S; ANTINEOPLASTIC AGENTS
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THE NON-HODGKIN'S LYMPHOMAS constitute a diverse group of malignancies of the lymphoid system, collectively representing approximately 4% of all cancer deaths in the United States.[1] The incidence of non-Hodgkin's lymphomas has been increasing during the past two decades, and it has been estimated that approximately 51 000 new cases will be diagnosed and 23 000 deaths will occur during 1995.[1] The median age for presentation is 42 years, and the incidence increases with advancing age.[2] The majority (75%)[2] of non-Hodgkin's lymphomas are of B-cell origin, although exceptions exist, such as Sézary's syndrome, mycosis fungoides, adult T-cell leukemia/lymphoma, and many cases of lymphoblastic lymphoma, which are diseases of T-cell origin. Although the non-Hodgkin's lymphomas are diverse in their responses to therapy and their natural histories, their origin involves a common theme: they represent a clonal malignant expansion of lymphocytes that appear to be arrested at a specific stage of normal lymphocytic differentiation.[3] The precise etiology of the non-Hodgkin's lymphomas is unknown, despite considerable advances in understanding the biology of this disorder during the past decade.

A viral origin is suspected and, indeed, it has been shown that adult T-cell lymphoma has a viral etiology. Moreover, Epstein-Barr virus has been convincingly related to the etiology of African Burkitt's lymphoma and to posttransplant lymphomas, as well as to some lymphomas arising in patients with acquired immunodeficiency syndrome (AIDS).

The clinical behavior of most non-Hodgkin's lymphomas may be broadly categorized into two

ABBREVIATIONS

ACOP-B: low-dose doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin
ABMT: autologous bone marrow transplant
ADA: adenosine deaminase
AIDS: acquired immunodeficiency syndrome
ara-C: cytosine arabinoside (cytarabine)
BACOP: bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone
bcl-2: B-cell leukemia/lymphoma
CALGB: Cancer and Leukemia Group B
2-CdA: 2-chlorodeoxyadenosine (cladribine)
CD8 cells: mature T-suppressor/cytotoxic cells
CD10: common acute lymphoblastic leukemia antigen (CALLA)
CD34 cells: mature T-helper cells
CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone
CHOP-Bleo: cyclophosphamide, doxorubicin, vincristine, prednisone and bleomycin
CHVP: cyclophosphamide, doxorubicin, teniposide, and prednisone
CLL: chronic lymphocytic leukemia
C-MOPP: cyclophosphamide, vincristine, procarbazine, and prednisone
CNS: central nervous system
COMLA: cyclophosphamide, vincristine, methotrexate with leucovorin rescue, and ara-C
COPA: cyclophosphamide, doxorubicin, vincristine, and prednisone
CR: complete response
CT: computed tomography
CTCL: cutaneous T-cell lymphoma
CVP: cyclophosphamide, vincristine, and prednisone
DCF: 2′-deoxycoformycin (pentostatin)
DHAP: dexamethasone, high-dose ara-C, and cisplatin
ECOG: Eastern Cooperative Oncology Group
F-ara-ATP: fluoro-arabinofuranosyl-adenosine triphosphate
2-F-ara-A: 2-fluoro-arabinofuranosyl-adenine
GELA: Multicenter Cooperative Groupe d'Etude des Lymphomes de l'Adulte
Gy: gray
HIV: human immunodeficiency virus
HLA: human lymphocyte antigen
HTLV-I: human T-cell leukemia/lymphoma type I
I-COPA: cyclophosphamide, doxorubicin, vincristine, prednisone, and rHuIFN-α
rHuIFN-α: recombinant human interferon alfa
rHuIFN-α2a: recombinant human interferon alfa-2a
rHuIFN-α2b: recombinant human interferon alfa-2b
rHuIFN-αn1: highly purified blend of natural human interferons
LDH: lactic dehydrogenase
MACOP-B: methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin
MALTomas: *m*ucosa-*a*ssociated *l*ymphoid *t*issue lymphomas
m-BACOD: methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone,
MU: million units
PCA: polyclonal antibody
PR: partial response
ProMACE-CytaBOM: prednisone, methotrexate, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue
ProMACE-MOPP: prednisone, methotrexate, doxorubicin, cyclophosphamide, and etoposide alternating with nitrogen mustard, vincristine, procarbazine, and prednisone
SWOG: Southwest Oncology Group
VABE: etoposide, doxorubicin, vincristine, prednisone, and bleomycin
VMP: etoposide, mitoxantrone, and prednimustine
Working Formulation: National Cancer Institute's Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage

TABLE 1
CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS*

Working Formulation	Rappaport classification
Low-grade	
Malignant lymphoma, small lymphocytic consistent with chronic lymphocytic leukemia	Diffuse well-differentiated lymphocytic (DWDL)
Malignant lymphoma, follicular predominantly small cleaved cell	Nodular poorly differentiated lymphocytic (NPDL)
Malignant lymphoma, follicular mixed, small cleaved and large cell	Nodular mixed lymphocytic-histiocytic (NH)
Intermediate-grade	
Malignant lymphoma, follicular predominantly large cell	Nodular histiocytic (NH)
Malignant lymphoma, diffuse small cleaved cell	Diffuse poorly differentiated lymphocytic (DPDL)
Malignant lymphoma, diffuse mixed, small and large cell	Diffuse mixed lymphocytic-histiocytic (DM)
Malignant lymphoma, diffuse large cell	Diffuse histiocytic (DH)
High-grade	
Malignant lymphoma, large cell, immunoblastic	Diffuse histiocytic (DH)
Malignant lymphoma, lymphoblastic	Diffuse lymphoblastic (LL)
Malignant lymphoma, small noncleaved cell	Diffuse undifferentiated (DU)

*Adapted from Gaynor and Fisher, reference 3, with permission

groups: the favorable, indolent lymphomas and the unfavorable, aggressive lymphomas. The former group has a longer natural history, with patients enduring slowly progressive disease over a span of many years. This category of non-Hodgkin's lymphoma, which is not usually curable, includes diffuse well-differentiated lymphocytic lymphoma, nodular mixed, and nodular poorly differentiated lymphocytic lymphomas. On the other hand, the unfavorable or aggressive lymphomas tend quickly to progress to death in the absence of therapy. Treatments have recently been developed that can provide long-term (disease-free) survival for many of these patients. The unfavorable, aggressive non-Hodgkin's lymphomas include nodular histiocytic, diffuse mixed, diffuse histiocytic, diffuse undifferentiated, and diffuse poorly differentiated lymphocytic lymphomas.

Several histologic classifications of non-Hodgkin's lymphoma[4–6] have been widely used during the past several decades. However, this has resulted in confusion about the diagnosis of the disease. The Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage[7] (the Working Formulation) was developed in order to permit a meaningful correlation among the principal histologic classifications of non-Hodgkin's lymphoma (*Table 1*). The Working Formulation organizes the non-Hodgkin's lymphomas into three subtypes (low, intermediate, and high grades) and categorizes them according to natural history and potential response to therapy. Despite the consistency provided by the Working Formulation, the classification of this disease remains imperfect, as is reflected by the fact that several "new" subgroups of non-Hodgkin's lymphoma have been identified that do not fit well into the Working Formulation. These include, for example, low-grade lymphomas such as monocytoid B-cell lymphoma[8]; low- and intermediate-grade lymphomas such as mantle zone lymphomas[9]; intermediate- and high-grade lymphomas such as anaplastic large-cell lymphoma[10]; and the cutaneous T-cell lymphomas (CTCLs), mycosis fungoides, and Sézary's syndrome.[11]

During the past decade, considerable progress has been made in our understanding of the biologic basis and approach to treatment of non-Hodgkin's lymphomas. This diverse group of malignant lymphomas exhibits distinctive natural histories and responses to treatment. In general, the non-Hodgkin's lymphomas are responsive to treatment, although the extent and duration of the responses may vary considerably. It is of great importance to establish a correct histologic diagnosis in order to assure that the most appropriate therapeutic plan is offered to each individual patient. General treatment options are schematically represented in the *Figure*.

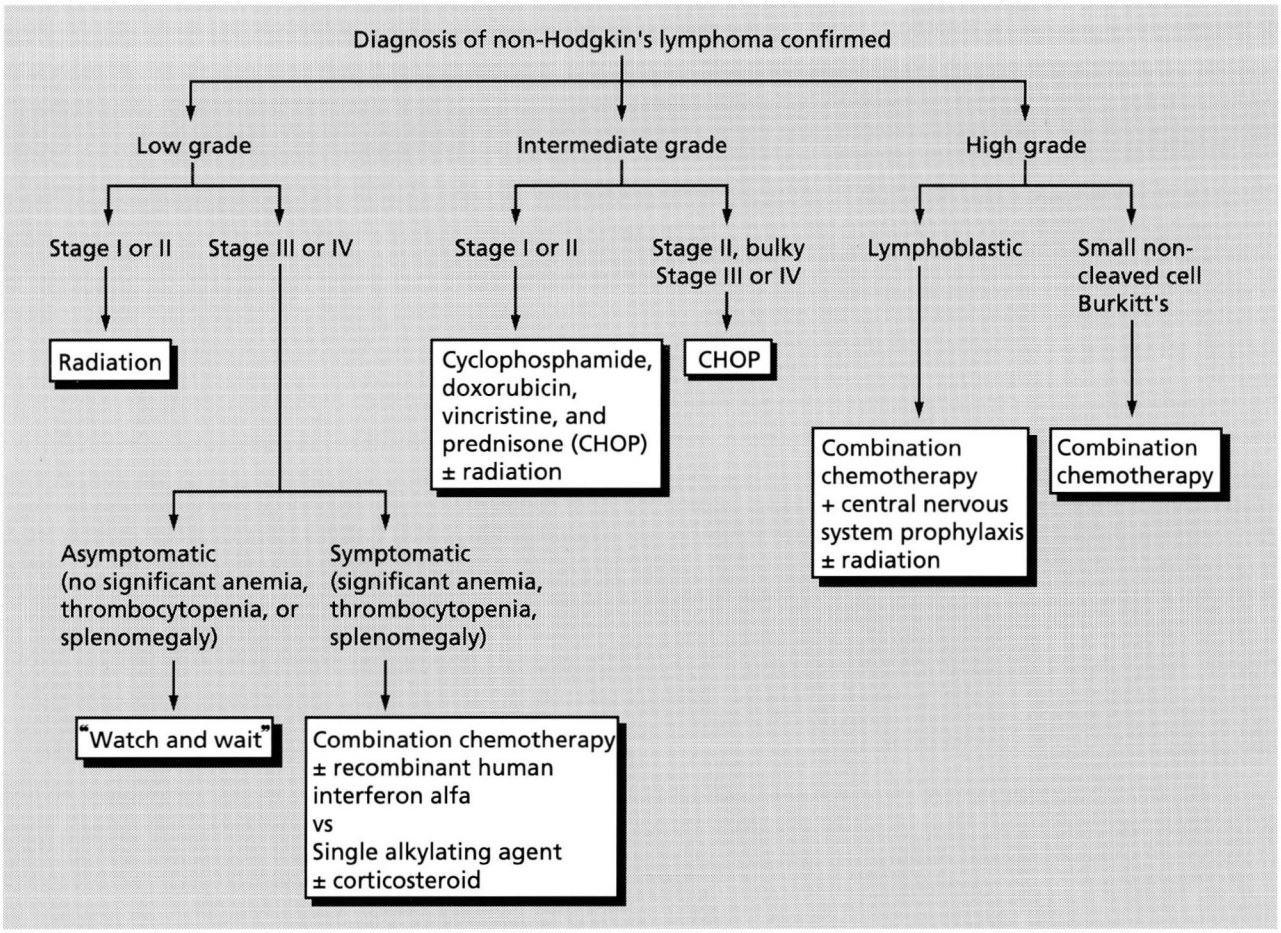

FIGURE. Schematic representation of general treatment options for non-Hodgkin's lymphoma. See also Table 6.

PATHOPHYSIOLOGY OF NON-HODGKIN'S LYMPHOMAS

Cytogenetic and molecular genetic analyses of malignant lymphocytes provide strong experimental evidence for the clonal origin of human lymphoid neoplasms.[12–23] Clonal expansion of B cells or T cells in the non-Hodgkin's lymphomas refers to a situation in which, presumably, a single cell has undergone malignant transformation, giving rise to a clone of identical B or T cells. The progeny commonly recapitulate the functional and phenotypic characteristics of the normal B or T cell at the corresponding stage of development. Because the rearrangement of antigen receptor genes takes place early during the differentiation of B or T lymphocytes, rearrangements of one or more antigen receptor genes are found in almost all human lymphoid neoplasms.[19–25]

To suitably accomplish the process of immune recognition, antigen receptor genes (immunoglobulin and T-cell receptor genes) must undergo rearrangement of their DNA prior to encoding key proteins. Such rearrangement has been described in detail.[26] Rearrangement of immunoglobulin genes is generally restricted to cells of the B-cell lineage, whereas gene rearrangement in T cells involves a different set of genes, namely those encoding T-cell antigen receptors.[27] The genomic structure of the T-cell antigen receptor genes is very similar to that of the immunoglobulin genes. Accordingly, T-cell receptor genes undergo rearrangement through joining of V-J or V-D-J segments during early T-cell differentiation, thereby providing great diversity of antigen recognition by the T cell. The immunoglobulin gene rearrangements may serve as unique clonal markers[21] in human lymphoid neoplasms because, as a clonal expansion, an individual tumor

contains the identically rearranged gene throughout the cell population. Moreover, a gene rearrangement discovered in a lymphoid cell population not only indicates clonality but in most situations may also provide a lineage marker.[23] In order to detect such gene rearrangements, DNA is extracted from tissue samples such as peripheral blood, bone marrow aspirates and biopsies, and lymph node biopsies. The DNA is cut[15] with a restriction endonuclease that identifies recognition sites that flank a selected part of the gene believed to have undergone rearrangement. The DNA that has been cut with the restriction enzyme and hybridized with selected probes will show altered restriction fragment sizes if rearrangement has occurred. Rearrangements of immunoglobulin genes can be demonstrated using Southern blot analysis in virtually all B-cell malignancies.[21,28]

During the past two decades, multiple studies have established that most human lymphoid neoplasms are associated with characteristic chromosomal abnormalities.[12,29–31] As mentioned above, the chromosomal abnormalities detected in non-Hodgkin's lymphoma have a clonal origin; therefore, the initial chromosomal variation takes place in a single cell, with subsequent cells carrying the identical variation. Such variations are thus somatic mutations in lymphoma patients with an otherwise normal karyotype. Clearly, non-Hodgkin's lymphoma is a genetic disease. Rowley[14] cites several landmark contributions that have paved the way for our understanding of the genetics of non-Hodgkin's lymphoma. These include the identification of extra chromosomal material on chromosome 14 (14q+) from patients with Burkitt's lymphoma,[32] the determination that the 14q+ was a result of translocation[33] between chromosomes 8 and 14, identification of the 14;18 translocation,[34] cloning of the translocation breakpoint junction from Burkitt's lymphoma,[35,36] and cloning of the t(14;18) junction.[37] These contributions made it possible to compare multiple characteristics of the non-Hodgkin's lymphomas, such as karyotype, histology, immunophenotype, and, more recently, DNA markers. In combination with data correlating these characteristics with the clinical response to treatment, it has become possible to demonstrate that different chromosomal profiles are associated with different natural histories and overall survival times in the non-Hodgkin's lymphomas.[38]

The most common chromosomal abnormality in the non-Hodgkin's lymphomas is the 14;18 translocation t(14;18), which was first reported in 1979 by Fukuhara et al,[34] who detected this translocation in six of nine patients with a diagnosis of poorly differentiated lymphocytic lymphoma. The 14;18 translocation is most common in the follicular lymphomas, although it may be seen in multiple histologic subtypes of non-Hodgkin's lymphoma. This translocation results in the rearrangement of a proto-oncogene, bcl-2 (B-cell leukemia/lymphoma), normally located on chromosome 18, with the immunoglobulin heavy chain region on chromosome 14. In the study of Yunis et al,[12] the t(14;18) translocation was detected in 60 of the 71 B-cell lymphoma patients (85%) studied. Among these patients, 37 were diagnosed with follicular small cleaved-cell, 17 with follicular mixed-cell, and 17 with follicular large-cell lymphoma. The 60 cases of translocation included all 37 of the patients with follicular small cleaved-cell lymphoma. In that group, 10 patients presented with t(14;18) as a single chromosomal defect and experienced an indolent disease course, with eight of 10 patients not requiring any treatment for 1 to 4 years after diagnosis. Those patients who did not exhibit a single chromosomal defect generally had from two to nine chromosomal defects. More than 70% of all the chromosomal defects detected in patients from this and the authors' preceding studies[30,31] were found to be recurrent. These defects included 14 distinct nonrandom chromosomal duplications and deletions. Most of these 14 defects correlated with a specific histopathology, poor prognosis, or leukemic blood picture, or a combination of these features. The authors proposed a model for the general evolution of follicular lymphomas carrying the 14;18 translocation. The model provides a suggested correlation between histopathology, chromosomal defects, and clinical aggressiveness of the disease. The bcl-2 oncogene rearrangement was confirmed in specimens from patients with follicular small cleaved-cell, mixed-cell, and large-cell lymphoma,[12] suggesting that the translocation with accompanying oncogene rearrangement may be a crucial requirement for the follicular process.

Ngan et al[17] further demonstrated the consistent expression of a proto-oncogenic protein, bcl-2, in a large proportion of non-Hodgkin's lymphomas and proposed that t(14;18) translocations might have as a common consequence the overexpression of the bcl-2 protein product. They raised antibodies

against the bcl-2 gene protein product that were shown to specifically recognize a human protein whose presence correlated with transcription of the bcl-2 gene. They used the antibodies to demonstrate that the bcl-2 protein is expressed in a substantial proportion of non-Hodgkin's lymphomas at levels sufficiently high to permit detection by frozen-section immunohistochemistry. The bcl-2 protein was not detected in all of the malignant lymphomas studied, nor was it found in normal or reactive lymphoid tissue; expression of the bcl-2 protein was most commonly associated with non-Hodgkin's lymphomas exhibiting the t(14;18) translocation. Conversely, a small number of lymphomas lacking evidence of the t(14;18) translocation did express the bcl-2 protein at comparable levels to those associated with cells bearing the translocation. It is possible that such neoplasms did actually contain t(14;18) translocations with breakpoints outside the regions detected by the DNA probes employed. Also, the expression of bcl-2 was most prevalent in follicular lymphomas, with measurable bcl-2 protein found in virtually all the small cleaved-cell follicular tumors. By contrast, a lesser proportion of follicular large-cell tumors expressed measurable bcl-2 protein. This is not surprising because a substantially lower percentage of follicular large-cell neoplasms exhibit the t(14;18) translocation.[16] By preventing apoptosis or programmed cell death, overproduction of the bcl-2 gene protein product plays a role in perpetuation of the cancerous cell clone.

The t(14;18) chromosomal translocation is by no means the only rearrangement of great significance in human lymphoid neoplasia. Chromosomal rearrangements involving translocation to the terminal regions of the long arm of chromosome 14 have been detected in a variety of tumors with involvement of chromosomes 8, 11, or 18 as "donor" chromosomes.[15] One of the most thoroughly characterized groups of chromosomal abnormalities comes from patients with Burkitt's lymphoma. Cytogenetic and molecular genetic techniques have demonstrated that translocations of chromosomes 8 and 14 are very common in this disease, and translocations of genetic material between chromosomes 2 and 8 and chromosomes 8 and 22 occur much less frequently. Each of these translocations involves juxtaposition of a gene coding for a segment of the immunoglobulin molecule and a gene located on chromosome 8, which codes for the c-*myc* proto-oncogene, the human homologue of the retroviral v-*myc* oncogene.[36] In Burkitt's lymphoma, the most common translocation, t(8;14), involves the c-*myc* gene undergoing translocation from its normal location on chromosome 8 to the immunoglobulin heavy chain locus on the long arm of chromosome 14. By contrast, in the other translocations cited above (t[2;8] and t[8;22]), an immunoglobulin light chain locus becomes adjacent to c-*myc*. It is believed that such rearrangements expose the c-*myc* proto-oncogene to the influence of regulatory sequences in or near the immunoglobulin locus. This event might, in turn, deregulate expression of the *myc* gene and contribute to potentiation of B-cell neoplasia. Finally, other translocations involving chromosome 14 are encountered in human lymphoid neoplasms,[39] such as the t(11;14) chromosome translocation, which is seen in mantle zone lymphomas. In such instances, the breakpoint on chromosome 14 occurs in the region carrying the heavy chain locus. Tsujimoto et al[39] studied diffuse large-cell lymphomas and chronic lymphocytic leukemia (CLL) cells of the B-cell type carrying the t(11;14) translocation in order to clone the chromosomal breakpoint to obtain nucleic acid probes that would permit identification of a putative oncogene that might be activated by translocation to the heavy chain locus. This gene, named bcl-1, appears to have a role in the malignant transformation of human B-cells exhibiting the t(11;14) translocation.

In general terms, the non-Hodgkin's lymphomas constitute a diverse group of diseases involving clonal expansions of B or T lymphocytes arrested at a specific stage of cell maturation. Although the molecular mechanisms underlying these events are not clearly understood, the chromosomal translocations cited above appear to confer a neoplastic proliferative advantage in the non-Hodgkin's lymphomas.

During the past decade, our understanding of the immunophenotypes of the normal cells of the immune system has increased. Lymphocytes may be functionally categorized into specific populations by virtue of their expression of unique cell surface markers. Normal B-cell differentiation begins at the level of the lymphoid stem cell and proceeds through multiple stages, namely pre–B-cell, mature or resting B-cell, activated or proliferative B-cell, differentiating B-cell, and finally, the appearance of the plasma cell. These stages of normal B-cell ontogeny are characterized by the expression of unique cell-surface and cytoplasmic antigens. Some of the antigens are found only at a specific level of B-cell differentiation,

whereas others, so-called pan–B-cell antigens, are present during multiple levels of differentiation. However, a sequential loss of pan–B-cell antigens occurs during the differentiation process. Certain antigens are particularly helpful in elaborating B-cell lineage because their expression is confined to B lymphocytes—for example, CD19, CD20, and CD24. The pre-B cell typically expresses the CD10 antigen, which is not expressed during further maturation of the lymphocyte series beyond the pre–B-cell stage. CD10 is also referred to as CALLA, the common acute lymphoblastic leukemia antigen. At the stage of the resting B lymphocyte, expression of CD19, CD20, and CD24 continues, and these cells begin to express surface immunoglobulins, IgD and IgM as well as CD21, CD22, and CD35. The CD21 antigen is the receptor for the Epstein-Barr virus. Multiple surface antigen changes occur on lymphocytes as they traverse the stage of development from the resting B cell to the activated-proliferating B cells. About the time that loss of CD21 and CD22 antigens takes place, a host of activation antigens appear that are presumed to have a key role in the further differentiation of B lymphocytes. B-cell–associated activation antigens include, among others, CD5, CD23, CD35, and CD71. CD71 is the transferrin receptor. Finally, at the stage of development of the secretory B cell, CD38 and PCA-1 appear, whereas by that time there has already been a loss of the B-cell activation antigens and the pan–B-cell antigens.

The cell surface phenotypic markers described above are useful in the diagnosis of the non-Hodgkin's lymphomas. As noted earlier, approximately 75% of non-Hodgkin's lymphomas are of B-cell origin. Virtually all of these express the pan–B-cell antigens such as CD19, CD29, and Ia, as well as one or more B-cell activation antigens. The cell surface antigenic phenotype has value in the diagnosis of B-cell lymphomas; however, it should be mentioned that considerable antigenic heterogeneity is present within the histologically defined subgroups of this disease. A wide variety of monoclonal antibodies has been used in the diagnosis of B-cell lymphomas.

Even though most researchers typically relate the B-cell non-Hodgkin's lymphomas to the principal stages of B-lymphocyte development, it is now clear that these neoplasms correspond to specific subpopulations of activated-proliferating B lymphocytes. Among the low-grade subtype of non-Hodgkin's lymphoma, the follicular small cleaved-cell lymphomas are believed to correspond to specific subpopulations of germinal center B cells, and these tumors express CD10, CD21, B5, and the pan–B-cell antigens. By contrast, the low-grade small lymphocytic subtype of non-Hodgkin's lymphoma, which is the tissue counterpart of B-cell CLL, corresponds to a subpopulation of activated B cells expressing CD5, CD21, B5, and the pan–B-cell antigens. Among the intermediate-grade subtype of non-Hodgkin's lymphoma, the follicular large-cell and the diffuse large-cell varieties express multiple B-cell activation antigens as well as the pan–B-cell antigens. However, the follicular large-cell lymphoma expresses CD10, whereas the diffuse large-cell intermediate-grade subtype non-Hodgkin's lymphoma does not express CD10. Among the high-grade subtype of non-Hodgkin's lymphoma, the immunoblastic variety is clinically indistinguishable and phenotypically very similar to the intermediate-grade B-cell diffuse large-cell lymphoma. Also included in the high-grade small non-cleaved-cell subtype is Burkitt's lymphoma, which commonly expresses B-cell activation antigens as well as CD10.

As mentioned above,[3] immunophenotypic clonality in the family of B-cell lymphoid neoplasms is usually clear-cut because the majority of cells express a heavy chain and a light chain on their surfaces or in the cytoplasmic compartment, thereby providing evidence of a monoclonal nature. Among the T-cell lymphomas, there is not an analogous standard for monoclonality. Numerous monoclonal antibodies have been developed in order to detect and define cell surface antigens expressed on human T cells. T cells derive from the thymic environment, where they undergo development prior to expulsion into the circulation and peripheral lymphatic tissues. During the three principal stages of T-cell differentiation in the thymus, there is a significant change in the spectrum of cell surface antigens. During the first stage of T-cell differentiation (the prothymocyte stage), CD2, CD7, CD38, and CD71 are expressed. Transition to stage 2 involves the loss of expression of CD71 and the appearance of expression of CD1, CD4, and CD8. During stage 3 of T-cell differentiation, the cells may lose CD1 while acquiring CD3, CD5, and CD6. Cells at this stage of T-cell development also express the T-cell antigen receptor. Following completion of stage 3 intrathymic maturation, the T cells depart the thy-

mus, where they are broadly categorized as expressing either CD4 or CD8.

Mature peripheral T cells that undergo activation exhibit other changes in expression of surface antigens. T-cell lymphomas also reflect specific stages of T-cell differentiation, and in the same sense as B-cell lymphoid neoplasms, substantial heterogeneity may be seen within histologically defined subtypes. High-grade lymphoblastic non-Hodgkin's lymphomas usually exhibit a T-cell immunophenotype (approximately 95% of cases) and correspond to stage 2 thymocytes in the sequence of T-cell differentiation. Most of the other T-cell lymphomas have been reported to correspond to mature T-helper (CD4) cells or mature T-suppressor/cytotoxic (CD8) cells. Such lymphoblastic non-Hodgkin's lymphomas present with a diffuse growth pattern and occur in patients with a median age of approximately 17 years, which is considerably younger than the median age of patients with low-, intermediate-, or other high-grade non-Hodgkin's lymphomas.

GENERAL CLINICAL FEATURES

Approximately two thirds of patients with non-Hodgkin's lymphomas typically present with persistent and painless superficial lymphadenopathy. Only approximately 20% of patients with non-Hodgkin's lymphoma present with systemic symptoms (ie, B symptoms), in contrast to an approximate 40% incidence of systemic symptoms among patients initially presenting with Hodgkin's disease. Also, approximately 20% of patients with non-Hodgkin's lymphomas exhibit mediastinal adenopathy. This is, of course, much less frequent than the same finding in patients with Hodgkin's disease. In many cases of non-Hodgkin's lymphoma, there is involvement of pelvic, mesenteric, and retroperitoneal lymph nodes, although it is usually not symptomatic. Among non-Hodgkin's lymphoma patients who present with mediastinal adenopathy, complaints of chest pain or an unremitting cough are not uncommon. Patients with large T-cell lymphomas and mediastinal lymphadenopathy may present with a superior vena cava syndrome. Lymphatic tissue throughout the body may be involved in the non-Hodgkin's lymphomas, including mesenteric, epitrochlear, and preauricular lymph nodes, as well as the tissues found within Waldeyer's ring. Approximately 20% of patients with non-Hodgkin's lymphoma present with palpable splenomegaly; in some cases, massive splenomegaly may exist. Also, bone marrow involvement in non-Hodgkin's lymphoma occurs in approximately one third of patients, although there is significant variation in the incidence of marrow involvement among the various histologic subtypes. During the early clinical phases of non-Hodgkin's lymphoma, most patients present with a normal peripheral blood picture; however, approximately one half of these patients will develop anemia as the disease progresses. The anemia seen in non-Hodgkin's lymphoma is typically due to one of or a combination of the following causes: hypersplenism, hemorrhage, autoimmune hemolytic anemia, marrow injury due to chemotherapy and/or radiation, and bone marrow replacement due to the disease. Lymphocytosis may be seen in some patients; however, the white blood cell count is frequently normal in this disease.

The initial clinical presentation in patients with non-Hodgkin's lymphoma includes extranodal disease in approximately 30% to 40% of patients. Only approximately 10% of patients presenting with indolent lymphomas have localized disease at initial diagnosis. The diffuse aggressive lymphomas much more commonly are associated with localized disease at initial clinical presentation. Compared with patients with diffuse aggressive lymphoma, those with indolent lymphomas are much more likely to present initially with hepatomegaly and bone marrow involvement. When jaundice is encountered, it usually reflects infiltration of the liver by malignant cells, although it may also result from extrahepatic biliary tract obstruction. Gastrointestinal tract involvement, whether as a primary or secondary site of disease activity, can be reflected by symptoms such as malabsorption, bleeding, obstruction, abdominal pain, and accompanying diarrhea. In some cases, frank perforation may occur as a result of tumor involvement.

Extranodal involvement in the non-Hodgkin's lymphomas may involve other tissues also; primary lesions have been described in the testes, thyroid, lung, bone, female reproductive tract, and other tissues. These extranodal presentations are more typically associated with the diffuse histiocytic lymphomas. Renal dysfunction usually reflects the presence of urinary outflow tract obstruction by tumor. The most frequent clinical manifestation of non-Hodgkin's lymphomas in the nervous system involves compression of the spinal cord due to extradural tumor mass. Involvement of the brain pa-

TABLE 2
THE ANN ARBOR STAGING CLASSIFICATION*

Stage I	Involvement of a single lymph node region (I) or of a single extralymphaticorgan or site (I_E)†
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S), or by localized involvement of an extralymphatic organ or site (III_E) or both (III_{SE})
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement

*Reprinted from Gaynor and Fisher, reference 3, with permission
†The subscript $_E$ denotes involvement of an extralymphatic site. Asymptomatic patients are denoted by the suffix $_A$; systemic symptoms (fever > 38°C, night sweats, weight loss > 10% of body weight) are denoted by the suffix $_B$

renchyma has historically been very rare as a site for primary non-Hodgkin's lymphoma; however, the AIDS epidemic may bring about a substantially increased frequency of non-Hodgkin's lymphoma as a primary brain tumor. Finally, the non-Hodgkin's lymphomas may present as primary skin neoplasms. Cutaneous T-cell lymphoma represents a malignant clonal proliferation of T lymphocytes predominantly of the CD4 phenotype. The principal presentations of this disorder are mycosis fungoides, which is a limited or generalized patchy or plaque-associated illness constituting approximately 90% of all CTCL patients, and Sézary's syndrome, which is a diffuse erythroderma with atypical circulating cells present in peripheral blood. The collective prevalence of these presentations is approximately 3000 to 4000 patients in the United States, with approximately 600 new cases reported each year. The clinical course of CTCL is usually indolent, especially for patients whose disease is confined to the skin.

As mentioned above, many patients with non-Hodgkin's lymphoma present with asymptomatic superficial lymphadenopathy. In comparison with patients with Hodgkin's disease, who typically present with fever, night sweats, weight loss, and other symptoms, it is uncommon for patients with the non-Hodgkin's lymphomas to exhibit these initial clinical signs and symptoms. Nonetheless, fever, night sweats, and weight loss as well as pruritus, anemia, gastrointestinal symptoms, bone pain, pleural effusion, and chylous ascites may be present relatively early on, depending on the level of aggressiveness of the disease. The differential diagnosis includes Hodgkin's disease, metastatic carcinoma, tuberculosis, acute and chronic leukemia, infectious mononucleosis, cytomegalovirus, infection by human immunodeficiency virus (HIV), and parasitic diseases, as well as other causes of lymphadenopathy. Although it is not possible to establish conclusively a diagnosis of non-Hodgkin's lymphoma in the absence of additional test results, some clinical characteristics do suggest this diagnosis—for example, the involvement of epitrochlear and mesenteric lymph nodes and Waldeyer's ring.

DIAGNOSIS AND CLASSIFICATION

The Ann Arbor staging classification is the most widely used system for staging of non-Hodgkin's lymphomas (*Table 2*). Originally developed for use in Hodgkin's disease, the Ann Arbor staging classification effectively provides an anatomic staging system in which the diaphragm serves as the principal landmark. The system incorporates information on the presence or absence of systemic symptoms such as fever, night sweats, and weight loss with the number of nodal or extranodal sites of tumor involvement. The prognostic value of the Ann Arbor staging classification system is greater for Hodgkin's disease than for the non-Hodgkin's lymphomas. In the former, disease typically spreads through contiguous groups of lymph nodes. By contrast, the non-Hodgkin's lymphomas typically exhibit hematogenous spread; accordingly, this staging system is less useful. Ostensibly, the Ann Arbor staging classification system is used to identify those patients with suspected non-Hodgkin's lymphoma who can be treated with localized therapy, although many

patients with suspected low-grade non-Hodgkin's lymphoma do not, after appropriate staging procedures have been conducted, exhibit only localized disease. Irrespective, however, of any deficiencies in application of the Ann Arbor staging classification to the non-Hodgkin's lymphomas, a thoroughly organized approach to staging is essential for any patient with a suspected diagnosis of non-Hodgkin's lymphoma.

TABLE 3
STAGING EVALUATION FOR NON-HODGKIN'S LYMPHOMAS*

Required for all patients
Detailed history and physical examination with thorough lymph node evaluation
Complete blood count, liver and renal function tests, serum protein electrophoresis, actic dehydrogenase, alkaline phosphatase
Chest roentgenogram
Computed tomography (CT) scan of abdomen and pelvis
Bilateral iliac crest bone marrow biopsies
Required or useful in selected circumstances
Thoracic CT scan, if chest roentgenogram abnormal
Liver biopsy
Radionuclide scans: bone, gallium, liver, spleen
CT scan of head
Chromosomal analysis
Gene rearrangement analysis
Cell surface markers
Magnetic resonance imaging
Abdominal ultrasound
Lymphangiogram

*Adapted from Gaynor and Fisher, reference 3, with permission

The diagnostic evaluation of patients with suspected non-Hodgkin's lymphoma is designed to establish the stage of the disease and to specify sites of tumor involvement to best assess the patient's response to treatment (*Table 3*). In addition to the initial excisional biopsy and subsequent documentation of the pathology and immunology related to that biopsy, the diagnostic evaluation should include the following items: a detailed history and physical examination; complete blood counts and blood chemistries, including renal and liver function tests, serum protein electrophoresis, serum lactate dehydrogenase, and serum alkaline phosphatase; a chest roentgenogram to rule out the presence of hilar or mediastinal lymphadenopathy, pleural effusions, and other pulmonary involvement; a chest computed tomography (CT) scan in the event of an abnormal chest roentgenogram; CT scans of the chest, pelvis, and abdomen to assess possible lymphadenopathy in the mesenteric and retroperitoneal nodes; and bilateral iliac crest bone marrow biopsies. In the event of significant hepatomegaly, a positive liver scan, or abnormally elevated liver function test levels, a liver biopsy should be carried out. Also, pathology studies involving morphologic evaluation of tissues should be conducted by a competent hematopathologist. Additionally, under certain conditions, for instance, where spread to bone or lower limb lymphatics is suspected, other staging studies based on patient symptoms and availability of diagnostic procedures should be conducted, including bilateral lymphangiograms of the lower extremities, bone scans and gallium scans, magnetic resonance imaging studies, and CT scans of the head, as well as additional studies of gene rearrangements and cell surface markers. A staging laparotomy is rarely recommended in non-Hodgkin's lymphoma because of its high morbidity and because other studies should sufficiently reflect the clinical state of the patient.

The pathologic classification of the non-Hodgkin's lymphomas has been a source of confusion for clinicians and histopathologists for many years, partly because at least six separate classification systems exist for this disease. The Rappaport Classification is the most widely used system in the United States and was first published almost 30 years ago.[4] According to the Rappaport Classification system, the non-Hodgkin's lymphomas are divided into two principal subtypes: nodular or follicular lymphomas and diffuse lymphomas. In the former group, the lymphomatous tissue retains certain morphologic characteristics of normal lymph nodes, whereas in the diffuse lymphomas, the normal cortical and paracortical lymph node morphology is obliterated. It also segments the non-Hodgkin's lymphomas into subdivisions based on whether or not the malignant

cells are well differentiated, poorly differentiated, histiocytic, or undifferentiated. The Rappaport Classification has undeniable merit, not only because it was the first established classification system for the non-Hodgkin's lymphomas and, as indicated above, the most widely used in the United States today, but also because it offers a classification system in which each histologically defined subgroup exhibits a unique and characteristic natural history and response to treatment. Nonetheless, advances in contemporary immunobiology have shown that the Rappaport Classification system has several defects. For example, the term "histiocytic" cells of the Rappaport Classification is a misnomer because most of the tumors are actually large transformed lymphocytes.

Less than a decade following introduction of the Rappaport Classification, the Lukes-Collins[5] and Kiel[6] classifications for the non-Hodgkin's lymphomas appeared, and by 1980, there were at least a half dozen separate classification systems. The accompanying confusion resulted in development of the Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage,[7] an attempt to provide a consistent language for classification of the lymphomas. The Working Formulation, introduced in 1982, has succeeded as a tool for the correlation of several histologic classifications of the non-Hodgkin's lymphomas. The Working Formulation classifies these diseases by their natural histories and responses to treatment. It does not use the term "histiocytic," referring instead to "large cells." Both the Working Formulation and the Rappaport Classification separate these diseases into groups based on morphology of the involved lymph nodes. The nodular pattern in the Rappaport Classification is referred to as follicular in the Working Formulation, whereas diffuse patterns are described identically (as diffuse) in both systems. Also, both classification systems segregate the non-Hodgkin's lymphomas according to the size of the predominant malignant cell. *Table 1* compares the Working Formulation and Rappaport Classification and clearly indicates the ease of translating one classification system into the other. In the Rappaport Classification scheme, the term "lymphocytic" is used when the cells of interest are small; in the Working Formulation, by contrast, the straightforward "small" is used to describe such cells.

Not long after publication of the Working Formulation in 1982, several subtypes of non-Hodgkin's lymphoma were reported that did not appear to fit into the subdivisions of the Working Formulation. These include, for example, *m*ucosa-*a*ssociated *l*ymphoid *t*issue lymphomas (the so-called MALTomas), a group of low-grade lymphomas commonly involving extranodal tissue such as the gastrointestinal tract, skin, breast, and thyroid gland. The clinical course of patients with these types of non-Hodgkin's lymphoma is typically that of a low-grade lymphoma. The monocytoid B-cell lymphomas constitute yet another group.[8] Patients afflicted with these types of non-Hodgkin's lymphoma are typically elderly women who initially present with disseminated disease. By contrast, mantle cell lymphomas refer to intermediate lymphocytic lymphomas that are of either the diffuse intermediate or mantle zone types.[9] Anaplastic large-cell lymphoma is usually of T-cell origin and, because of its anaplastic morphology, may be confused with carcinomas.[10] Patients with anaplastic large-cell non-Hodgkin's lymphoma frequently display the Ki-1 antigen and sometimes exhibit a t(2;5) chromosomal translocation. This type of non-Hodgkin's lymphoma appears to be relatively common in children, who typically present with extranodal disease, particularly of the skin.

Another non-Hodgkin's lymphoma that, in addition to the mantle cell lymphomas, MALTomas, and anaplastic large-cell lymphomas, does not fit well into the Working Formulation is adult T-cell leukemia/lymphoma, which is associated with infection by HTLV-I (human T-cell leukemia/lymphoma type I). This disease is more common in Japan, the Caribbean, and the southeastern United States and is often associated with hypercalcemia and a rapidly progressive clinical course.

Other non-Hodgkin's lymphomas that are cancers of T-cell origin and do not fit well into the Working Formulation include mycosis fungoides and Sézary's syndrome. Collectively, these two disorders are referred to as the CTCLs. From the standpoint of immunophenotype, the cancerous cells in these two diseases are mature helper (CD4) lymphocytes. Patients with these diseases do not exhibit symptoms reflecting excessive levels of helper T cells and are often misdiagnosed because their plaque-like skin lesions, which may be generalized or highly localized, may be misinterpreted as psoriasis prior to histologic evaluation. Alternatively, certain patients have more readily identifiable cutaneous tumors or generalized erythroderma. In the

CTCLs, the cancerous cells are believed initially to colonize skin, with subsequent invasion of lymphatic channels and viscera. In patients with very limited focal plaque skin disease, one is less likely to encounter evidence of visceral involvement compared with patients who present with generalized erythroderma, in which typically there is convincing evidence of extracutaneous disease. Patients who exhibit visceral disease have the worst prognosis of patients with CTCLs; it is rare to encounter visceral disease in the absence of lymph node involvement in these patients. In general, the CTCLs are considered indolent lymphomas, in which for most patients disseminated disease is the rule at the time of initial clinical diagnosis. Also, the CTCLs may be confused with the generalized skin lesions occurring in adult T-cell leukemia/lymphoma. One can usually distinguish between mycosis fungoides/Sézary's syndrome and adult T-cell leukemia/lymphoma by virtue of the fact that, in the latter, hypercalcemia, opportunistic infections, lung and bone tumor involvement, and early age of onset frequently exist, whereas these are seldom seen in the CTCLs. Unfortunately, because adult T-cell leukemia/lymphoma may exhibit a wide variety of histologic features, histopathology is often not particularly useful in establishing an accurate diagnosis.

As mentioned, the tumor stage of patients with aggressive non-Hodgkin's lymphoma is presently determined by the Ann Arbor staging classification system (originally developed for use in Hodgkin's disease), even though applying the system to the non-Hodgkin's lymphomas might not provide great accuracy in the identification of prognostic subgroups of patients. The International Non-Hodgkin's Lymphoma Prognostic Factors Project was conducted to develop a predictive model for determining outcome in patients with aggressive non-Hodgkin's lymphoma on the basis of clinical characteristics prior to treatment.[40] Sixteen academic institutions and oncology cooperative groups in the United States, Canada, and Europe participated in the project, which involved an evaluation of adult patients for clinical features that would predict overall survival and relapse-free survival. The patients were treated between 1982 and 1987 with combination chemotherapy regimens containing doxorubicin. Step-down statistical regression methods were employed to develop statistical models for the association of prognostic factors with overall survival and relapse-free survival among patients with complete responses (CRs). Clinical characteristics associated with overall survival and relapse-free survival were identified in multivariate analyses by proportional-hazards regression. Those features that remained independently significant according to the regression analyses of survival were incorporated into models identifying groups of patients of all ages, as well as groups of patients not more than 60 years old with different risks of death.

The authors developed two models. The first, the International Index, is applicable to all the patients studied and incorporates clinical features reflecting the growth and invasive potential of the tumor (tumor stage, serum LDH level, and number of extranodal disease sites), the patient's symptoms from the tumor (performance status), and the patient's ability to tolerate intensive therapy (age and performance status). For patients 60 years or younger, an age-adjusted model was developed and is referred to as the Age-Adjusted International Index.[40] This employs a subgroup of clinical features including tumor stage, serum LDH level, and performance status. Both the International Index and the Age-Adjusted International Index models identified risk groups of patients, based on both the rate of CR and the rate of relapse from CR. In the evaluation of more than 2000 patients of all ages, the model identified four risk groups with predicted 5-year survival rates of 73%, 51%, 43%, and 26%. In the age-adjusted model (patients 60 years or younger), four other risk groups were also identified and had predicted 5-year survival rates of 83%, 69%, 46%, and 32%. The authors[40] noted that in both predictive models, the increased risk of death was due to a lower rate of CR as well as to a higher rate of relapse from CR. They determined that the two indices were significantly more accurate than the Ann Arbor staging classification in predicting long-term survival in patients with aggressive non-Hodgkin's lymphoma. The authors proposed that clinical prognostic factor models such as the International Index and the Age-Adjusted International Index be used to identify specific risk groups and to compare different treatment modalities in patients with aggressive non-Hodgkin's lymphoma. Even though these indices were specifically developed for aggressive non-Hodgkin's lymphoma, they might have significant utility as predictive models for patients with more indolent disease. This is exemplified by a report[41] from France that evaluated the prognostic factors in patients with follicular lymphomas.

Even though the predictive model for aggressive non-Hodgkin's lymphoma proposed by the International Non-Hodgkin's Lymphoma Prognostic Factors Project Group[40] has been rather widely embraced as a meaningful tool in the design of therapeutic trials and in the selection of appropriate treatment modalities for individual patients, it has not received universal acceptance. For example, it has been criticized because patients with AIDS-associated non-Hodgkin's lymphoma were not included. According to the authors of the predictive model, patients with AIDS-associated non-Hodgkin's lymphoma were excluded from the International Index because they have less favorable prognoses and tolerate chemotherapy poorly because of the presence of cytopenia and concurrent infections. Notwithstanding criticisms in this and other regards, the predictive model proposed by the International Prognostic Factors Group appears to represent a considerable improvement over staging alone.

In contrast with the indolent or low-grade lymphomas, the high-grade lymphomas have a clinically aggressive natural history and in the absence of treatment commonly cause death in less than 2 years from initial clinical presentation. Ironically, the aggressive, high-grade non-Hodgkin's lymphomas may offer a better prognosis than the indolent lymphomas if they are treated promptly and in an appropriate fashion. Many patients diagnosed with aggressive non-Hodgkin's lymphoma will be cured of the disease if a complete remission is achieved and sustained for at least 2 years.[42] There is considerable heterogeneity from an immunologic and histologic standpoint among the aggressive non-Hodgkin's lymphomas, which are categorized in the intermediate- and high-grade divisions of the Working Formulation.[43] The majority of these lymphomas appear to be of B-cell origin, and it is likely that many are derived from low-grade B-cell neoplasms. In this regard, it is well known that multiple-site biopsies obtained at initial patient presentation may show more than one histologic appearance. For example, a high-grade lymphoma may be found at one anatomic site while an indolent lesion may be found at another.[44] Such histologic findings may have great clinical significance because, even though the high-grade lesion may successfully respond to treatment, the low-grade site may be more refractory. Thus a patient with these findings may experience relapse with a low-grade lymphoma. This situation underscores the great importance of extensive and accurate histologic evaluation of patients with non-Hodgkin's lymphoma.

Approximately 20% of the aggressive non-Hodgkin's lymphomas are of T-cell origin. They exhibit histologic heterogeneity and, according to the Working Formulation, principally comprise the subdivisions of diffuse, mixed small- and large-cell lymphoma, and large-cell immunoblastic lymphoma. These tumors respond to aggressive chemotherapy and, generally speaking, the response of high-grade T-cell lymphomas is approximately the same as that of B-cell lymphomas. As such, immunophenotype per se is not particularly useful in predicting whether or not a patient will respond to aggressive therapy.

According to the Working Formulation,[7] the indolent or low-grade lymphomas include the small lymphocytic lymphomas, follicular small cleaved-cell lymphoma, and follicular mixed small cleaved- and large-cell lymphoma. Almost 100% of the low-grade non-Hodgkin's lymphomas are of B-cell origin. These histologic diagnoses are usually associated with an indolent clinical course. Even though patients typically present with disseminated disease, the low-grade non-Hodgkin's lymphomas may have a comparatively long duration even without institution of aggressive chemotherapy. Although chemotherapy may halt tumor progression in the low-grade non-Hodgkin's lymphomas, it very rarely offers a cure. In addition to the low-grade non-Hodgkin's lymphomas mentioned above, other subtypes that do not comfortably fit into the subdivisions of the Working Formulation and that are more aggressive than the classic indolent lymphomas include diffuse intermediate lymphocytic lymphoma and its follicular variant, the mantle zone lymphoma.

Diffuse intermediate lymphocytic lymphoma appears to be the equivalent of the centrocytic lymphoma in the Kiel Classification.[6] Despite its categorization by some investigators as an indolent lymphoma, diffuse intermediate lymphocytic lymphoma has a poorer prognosis than that seen in the low-grade lymphomas described in the Working Formulation.[45,46] Extensive histologic variation may exist among the indolent lymphomas, and more than one histologic subtype may be found in the same pathologic specimen or in different specimens. The most frequently encountered discordant pattern is the combination of diffuse large-cell lymphoma in the diagnostic lymph node biopsy and the presence of small cleaved-cell lymphoma in the bone marrow biopsy.[47]

A considerable number of clinical and pathologic characteristics have been identified as prognostic factors in the indolent non-Hodgkin's lymphomas[48–52] (*Table 4*). The strongest predictor of survival in the low-grade non-Hodgkin's lymphomas is the response to initial treatment.[52] Other characteristics associated with a favorable prognosis include the extent of helper T-cell host infiltrates,[53–55] a normal hemoglobin level,[48,52] and a limited Ann Arbor staging classification (Ann Arbor stage I or II).[48,49,51,52] Other favorable prognostic factors in low-grade lymphomas include the number of large cells and the degree of follicularity noted during histopathologic evaluation.

There is significant variation among pathologists in their quantification of large cells in follicular lymphoma and, as a result, many oncologists are not comfortable relying on the number of large cells in establishing a prognosis in such patients. Also, the degree of follicularity in the indolent non-Hodgkin's lymphomas at the time of diagnosis is considered to be equivocal as a prognostic factor: the determination of survival differences among patients displaying predominantly diffuse patterns vs those displaying predominantly follicular patterns may depend substantially on the treatment used. This is exemplified by the study of Hu et al,[56] which disclosed in a retrospective review that predominantly diffuse mixed lymphomas appear to have a significantly less favorable prognosis than do predominantly follicular lymphomas when the treatments involved mild chemotherapy. Unfavorable prognostic factors in the indolent lymphomas include, among others, absence of interfollicular fibrosis[41] and increased expression of certain nuclear proliferation antigens (eg, Ki-67) and the percentage of cells in S phase.[57] Elevated levels of serum lactic dehydrogenase and β_2-microglobulin, which are established prognostic determinants in aggressive non-Hodgkin's lymphomas, are also unfavorable prognostic factors in the indolent forms of the disease.

Patients with low-grade lymphomas exhibit considerable variability in clinical and histopathologic findings at the time of diagnosis. A predictive model for indolent non-Hodgkin's lymphomas, analogous to that described above for aggressive forms of the disease, would benefit the design of future clinical trials in patients with indolent disease and the selection of appropriate treatments for individual patients. Prognostic factor indices for stage IV follicular low-grade lymphoma,[50] as well as a prognostic index for all stages,[48] have been proposed. In addition, prognostic factors have been described for patients who relapsed during treatment of indolent non-Hodgkin's lymphoma[58]; the most predictive prognostic factors in these patients were initial response, age, and duration of response.

TABLE 4
PROGNOSTIC FACTORS IN THE INDOLENT NON-HODGKIN'S LYMPHOMAS*

Feature	Prognosis
Pathobiological	
Cytogenetic abnormalities	Unfavorable
Increased nuclear proliferation	Unfavorable
Helper T-cell infiltrates	Favorable
Absence of interfollicular fibrosis	Unfavorable
Mixed pattern (follicular plus diffuse)	Equivocal
Number of large cells	Equivocal
Clinical	
Normal hemoglobin	Favorable
Good performance status	Favorable
Limited Ann Arbor stage	Favorable
Age > 60	Unfavorable
Male	Unfavorable
Systemic symptoms	Unfavorable
Extranodal sites ≥ 2	Unfavorable
Bulky tumor	Unfavorable
Hepatosplenomegaly	Unfavorable
Elevated lactic dehydrogenase or β_2 microglobulin > 3 mg/day	Unfavorable
Bone marrow involvement > 20%	Unfavorable

*Adapted from Horning, reference 47, with permission

TREATMENT OF THE NON-HODGKIN'S LYMPHOMAS

The past decade has witnessed significant advances in our understanding of the biology and treatment of the non-Hodgkin's lymphomas. In a recent review article on the treatment of these disorders, Armitage[59] proposes that a physician seeing a new patient with non-Hodgkin's lymphoma should first consider the diagnosis, then prognosis, choice of treatment, and finally treatment itself.

As a general principle, the physician should be aware of the specific histologic diagnosis, the clinical extent of the lymphomatous involvement, and the patient's age and overall health. The great majority of patients with non-Hodgkin's lymphoma should receive chemotherapy with or without irradiation, as discussed below. Radiation therapy has only a very limited value as a primary treatment for most patients with non-Hodgkin's lymphoma. Sur-

gery is virtually never suggested as the sole treatment for patients with these diseases. Ostensibly, the ultimate treatment outcome is likely determined more by the disease stage and other prognostic factors than by the specific treatment regimen selected. Nonetheless, the non-Hodgkin's lymphomas in general are very responsive to chemotherapy and as a group are very radiosensitive. An accurate histologic and clinical evaluation is important to distinguish clearly between indolent and aggressive disease so that optimal chemotherapeutic and/or radiation treatment plans can be selected.

Stage I or II low-grade lymphomas

Patients with low-grade non-Hodgkin's lymphomas usually present with localized disease only after a complete clinical staging is conducted; in fact, only approximately 10% of patients with indolent lymphoma will be discovered to have stage I or II disease.[60] Such patients may benefit considerably from regional irradiation. While the frequency of curative irradiation in the non-Hodgkin's lymphomas is certainly low, it is likely that for selected patients who are accurately diagnosed as stage I or stage II, with nonbulky, contiguous disease, irradiation as sole therapy may produce a complete remission of considerable length. The prolonged disease-free survival of patients with stage I or II disease supports the position that, in the absence of additional prospective clinical data, regional irradiation is the standard treatment for such patients. An effort is made to limit the irradiation to areas of known disease, thus not damaging normal bone marrow that may be crucial for the patient's future ability to tolerate possible chemotherapy.

Stage III or IV low-grade lymphomas

Most patients diagnosed with low-grade lymphoma have advanced disease at the time of initial clinical presentation (stage III or IV). For such patients, there are many acceptable treatment options, although the likelihood of cure is low. Many of the treatment regimens produce a 60% to 75% rate of complete remission; however, such remissions are typically of short duration and, again, cure is rare. The median disease-free interval following the completion of treatment is only approximately 17 months. Following relapse, re-treatment may provide good results; however, the disease-free interval and complete remission rate decline with each re-treatment. Patients with stage III or IV indolent non-Hodgkin's lymphoma commonly survive with multiple episodes of recurrence. At 5 years, survival is approximately 80%, but this value falls to between 30% and 50% at 10 years.

Alkylating agents. Alone or in combination, alkylating agents have been the standard chemotherapeutic agents for the treatment of low-grade non-Hodgkin's lymphoma. They have been used for many years in the treatment of patients with advanced-stage indolent lymphoma. Chlorambucil administered at a daily oral dose of between 0.1 and 0.2 mg/kg or cyclophosphamide at a daily oral dose of 1.5 to 2.5 mg/kg is commonly used. The dose of each of these agents is titrated to maintain a platelet count greater than 100 000/mm^3 and a white blood cell count greater than 3000/mm^3. Such an approach to treatment may bring about clinical responses in a very slow fashion and, in fact, in some patients it takes 2 to 3 years in order to achieve a complete remission. The use of pulse chlorambucil in an oral dose of 16 mg/m^2 daily for 5 days may result in a much faster antitumor response compared with the use of daily oral chlorambucil.[61] With this approach, hematologic and other acute toxicities are relatively low; however, long-term daily alkylating agent treatment has been associated with an increased frequency of acute myelogenous leukemia in other disease states.

Combination chemotherapy. As an alternative to the use of chlorambucil or cyclophosphamide in the stage III or IV indolent non-Hodgkin's lymphomas, combination chemotherapy may be used. Two widely employed combinations are the CVP regimen and the C-MOPP regimen. The CVP regimen consists of cyclophosphamide (400 mg/m^2 by mouth daily for 5 days), vincristine (1.4 mg/m^2 intravenously on day 1), and prednisone (100 mg/m^2 by mouth daily for 5 days). In this regimen, treatment is repeated every 21 days and should be continued for a minimum of six cycles or, alternatively, for two cycles following attainment of a complete clinical response. The C-MOPP regimen consists of cyclophosphamide (650 mg/m^2 intravenously on days 1 and 8), vincristine (1.4 mg/m^2 intravenously on days 1 and 8), procarbazine (100 mg/m^2 by mouth on days 1 through 14), and prednisone (40 mg/m^2 by mouth on days 1 through 14. The C-MOPP regimen treatment cycle is repeated every 28 days.

It is important to underscore that in the treatment of the indolent non-Hodgkin's lymphomas, complete remissions may be achieved using a variety

of therapeutic regimens. The treating clinician may elect to administer a single alkylating agent, combination chemotherapy utilizing the CVP or C-MOPP regimen or other regimens, or alternative therapy such as total body or total nodal irradiation. Moreover, in some instances, a watch-and-wait approach may be preferred. Portlock and Rosenberg[62] at Stanford University have advocated a watch-and-wait approach for stages III and IV non-Hodgkin's lymphoma of indolent histologic types. A retrospective evaluation of the watch-and-wait approach compared with other treatment regimens disclosed that survival in the watch-and-wait patient group was approximately the same as that for patients who had received alternative treatment at the time of clinical diagnosis. Essentially, they demonstrated that asymptomatic patients may not need systemic treatment for several years following the initial diagnosis. Accordingly, it has been proposed that asymptomatic patients with advanced-stage indolent non-Hodgkin's lymphomas be observed and that treatment be implemented only when clearly indicated from the clinical standpoint. The watch-and-wait approach to the treatment of advanced-stage low-grade non-Hodgkin's lymphomas has been used frequently in the United States for the clinical management of such patients. The "watch" component of the watch-and-wait approach is very important. The clinician should evaluate these patients at least every 2 months to be assured that implementation of alternative therapy is not being neglected when essential. In any case, appropriate therapy involving drugs and/or irradiation should be promptly considered if a patient presents with evidence of extensive visceral or bone marrow disease. Total body irradiation may involve total doses of 150 to 300 Gy at a daily dose of 10 Gy. In such cases, routine monitoring for peripheral cytopenias is essential because thrombocytopenia is not uncommon. Alternatively, total nodal irradiation has been successfully applied in patients with stage III indolent disease. In making a determination of the optimal approach to treatment for a given patient with advanced-stage indolent non-Hodgkin's lymphoma, the physician should appreciate that with watchful waiting, the median time before therapy is required is approximately 3 years, and approximately 20% of patients do not require therapy for up to 10 years.[62] The overall median survival is approximately 11 years and the median 10-year survival is approximately 73%. Interestingly, it has been estimated that up to one fourth of such patients may show evidence of spontaneous disease regression in the absence of treatment. However, such an event is usually only a partial regression that is temporary in most cases.

The follicular, mixed small cleaved and large-cell variety of malignant lymphoma (nodular mixed lymphocytic-histiocytic cell) is considered by some to represent a unique subtype of low-grade non-Hodgkin's lymphoma. Optimal treatment for this variety is unclear at the present time, although it is common for oncologists to treat patients with this subtype in the same fashion as they treat patients diagnosed as having malignant lymphoma, follicular, predominantly small cleaved-cell disease (nodular poorly differentiated lymphocytic lymphoma). Longo et al[63] at the National Cancer Institute have reported that prolonged complete remissions are possible in such patients when treated with the C-MOPP regimen. By contrast, however, Glick et al[64] were unable to confirm a prolonged disease-free survival with combination chemotherapy.

In addition to the treatment regimens described above, some new and promising therapeutic approaches have been used for the indolent non-Hodgkin's lymphomas, including bone marrow transplantation, monoclonal antibody therapy, biologic therapies such as the use of recombinant human interferon alfa (rHuIFN-α), and several new chemotherapeutic agents.

Bone marrow transplantation. Bone marrow transplantation has emerged as a useful therapy which may lead to extended disease-free survival in a significant number of patients with relapsed low-grade non-Hodgkin's lymphomas.[65] Allogeneic bone marrow transplantation appears to have a role in the treatment of patients with small lymphocytic lymphoma consistent with CLL, and autologous transplantation appears to have merit in the treatment of low-grade follicular lymphomas. It is interesting to note that of the several thousand autologous bone marrow transplantation procedures conducted worldwide each year, non-Hodgkin's lymphoma is the disease most frequently treated.[66]

There has been considerable debate about the relative value of allogeneic vs autologous bone marrow transplantation in the treatment of patients with indolent lymphoma. Because patients with small lymphocytic lymphoma/CLL typically exhibit lymphomatous involvement of the bone marrow as well as circulating cancer cells, autologous bone marrow transplantation does not appear particularly

well suited to such patients. By contrast, patients with low-grade follicular lymphomas typically have a lesser incidence of marrow and peripheral blood tumor infiltration. Accordingly, an autologous bone marrow transplant or autologous peripheral stem-cell transplant appears reasonable for many of these patients. This is the case even considering that most patients with advanced-stage indolent non-Hodgkin's lymphomas do exhibit tumor involvement on bone marrow biopsy.

There is no universal agreement about the optimal timing of bone marrow transplantation for patients with low-grade non-Hodgkin's lymphoma. At present, the use of bone marrow transplantation is generally reserved for patients who have not exhibited a CR to other systemic treatment regimens. Because of the potential merit of this therapy in the treatment of indolent lymphomas, studies are being conducted to ascertain the role of bone marrow transplantation as primary therapy for such patients.[67] While there is no clear evidence that bone marrow transplantation cures indolent lymphomas, it does provide long disease-free remissions. The justification for its use as part of primary therapy seems rational when one considers that the histologic transformation to diffuse large-cell lymphomas seen in patients with indolent disease has commonly been associated with a very poor prognosis.

Many issues remain to be resolved in the use of bone marrow transplantation for patients with low-grade non-Hodgkin's lymphoma. The optimal treatment regimen for such patients has not yet been determined. To date, most high-dose preparative chemotherapeutic regimens have been accompanied by total body irradiation due to the high sensitivity of follicular non-Hodgkin's lymphomas to total body irradiation.[68] In addition to the need to discover the optimal high-dose preparative regimen, it will also be crucial to delineate the optimal timing of bone marrow transplantation as part of primary therapy or following relapse, just as it will be important to discern the best source of hematopoietic rescue. Undeniably, the critical question in regard to bone marrow transplantation is related to ultimate outcome.[69] This question cannot be answered until additional clinical trials have been conducted and carefully reviewed. Furthermore, allogeneic bone marrow transplantation appears to be curative in selected patients with small lymphocytic lymphoma/CLL.[70] In their study, Bandini et al[70] administered high-dose cyclophosphamide and fractionated total body irradiation with or without additional chemotherapy as a preparative regimen. The majority of patients exhibited a strong anticancer effect from the high-dose therapy. The authors[70] cite that in two of the patients, molecular biologic experiments disclosed no measurable evidence of residual disease. Results from the study of Rabinowe et al[71] also provide optimism. That group reported studies involving allogeneic or autologous bone marrow transplantation with purging in patients with CLL. The patients were pretreated with various chemotherapeutic agents to reduce tumor bulk and then were administered high-dose cyclophosphamide and total body irradiation immediately prior to the bone marrow transplantation. The results were positive in that the frequency of complete remission was high; however, the authors highlight the need for considerably longer patient follow-up to determine the outcome of this treatment.

Other reports describe favorable responses in patients with indolent non-Hodgkin's lymphomas who receive autologous bone marrow transplantation using purged marrow. For example, Freedman et al[72] at the Dana-Farber Cancer Institute reported 69 patients with low-grade non-Hodgkin's lymphoma who received autologous bone marrow transplantation during sensitive relapse or first partial remission. They found that patients who received bone marrow transplants during complete remission had superior clinical outcomes compared with those patients who exhibited active disease at the time of transplantation. Optimistic results with autologous bone marrow transplantation in the indolent non-Hodgkin's lymphomas have also been reported by Colombat et al,[73] Gribben et al,[74] and Schouten et al.[75] Collectively, the results of these studies are encouraging; however, the authors of the reports almost invariably highlight the fact that many questions remain unanswered about autologous bone marrow transplantation in this clinical setting.

Monoclonal antibodies. During the past 15 years, clinical investigators have explored the possible use of monoclonal antibody-based therapies in the treatment of non-Hodgkin's lymphomas.[76] To date, more than 200 patients with various hematologic malignancies have been treated with unconjugated monoclonal antibodies. Among these, more than 50 patients with low-grade B-cell non-Hodgkin's lymphomas have received such therapy.[77–83] The experience with monoclonal antibody-based therapies for the indolent lymphomas is relatively limited, but it

does seem plausible that such an approach holds promise for these diseases. Nonetheless, to date it has not yielded strongly positive results. Perhaps an explanation is that most of the patients who have been treated thus far with monoclonal antibody-based therapies had been enrolled in phase I clinical trials, had received extensive prior treatments, and had malignancies that were refractory to conventional therapies. What has been learned is that monoclonal antibodies can generally be administered safely to patients. Indeed, a number of individuals did exhibit transient clinical responses, and in some cases CRs occurred. Grossbard and Nadler[76] appropriately state that future clinical trials will need to include patients enrolled earlier in the course of their disease—that is, before they have developed tumor cell resistance to treatment and organ damage from extensive prior chemotherapy and/or irradiation. Moreover, the use of monoclonal antibodies in patients with bulky tumor masses may not be feasible. It is not unrealistic to project that the probable role of monoclonal antibody therapy in treatment of patients with indolent non-Hodgkin's lymphoma may be to complement existing chemotherapy and radiation regimens. As sole therapy, it seems rather unlikely that the use of monoclonal antibodies will provide cure in these patients.

Recombinant interferon. Another promising approach to the treatment of low-grade non-Hodgkin's lymphomas involves the administration of recombinant human interferon alfa (rHuIFN-α). Numerous clinical and laboratory studies conducted during the past decade have substantiated the impression that rHuIFN-α may be perceived as a mainstay in the treatment of a number of malignant diseases.[84–88] The biologic and clinical effects of the interferons appear to be mediated through distinct cellular receptors. The overall antitumor efficacy of interferon lies partly in its antiproliferative and immunomodulatory actions.[89,90] Despite intensive laboratory investigation during the past 20 years, the precise molecular mechanism explaining the antiproliferative actions of interferon is unclear. Following internalization of the interferon-receptor complex, interferon present within the cell appears to modulate a variety of biochemical processes by altering gene expression. For instance, IFN-α inhibits expression of the gene for the enzyme ornithine decarboxylase. Such an inhibitory effect on this key cellular regulatory enzyme may explain the impact of interferon on cell-cycle slowing and arrested cellular division during G_0. Interferon alfa also inhibits the expression of other genes, such as the c-*myc* and c-*fos* oncogenes. In fact, it has been proposed that IFN-α is a natural tumor inhibitory agent.[88] Maintenance of the antitumor effect of IFN-α requires continued drug exposure and results in a cytostatic form of tumor inhibition. Because of the cytostatic-type of tumor inhibition observed, rHuIFN-α is generally not curative in malignant diseases; however it does produce prolonged remissions in a relatively safe and tolerable fashion in a variety of diseases. Although the role of rHuIFN-α in the treatment of non-Hodgkin's lymphomas is not completely defined, a number of recent studies cited below provide support for its use, particularly in the indolent forms of the disease.

The earliest clinical trials were conducted before the emergence of rHuIFN-α. The "crude" interferon was obtained from buffy coats of donated blood and therefore lacked the clear advantages of purity and reproducible activity associated with the recombinant form. Early on, Merigan's group[91] reported favorable results in patients with nodular poorly differentiated lymphocytic lymphoma who received human leucocyte interferon with an initial dose of 2.5 million units (MU), which was escalated to 5 MU twice a day for 30 days. Shortly after that study was published, Gutterman et al[92] treated 11 lymphoma patients with human leucocyte interferon; the results confirmed those obtained by Merigan et al[91] and, more importantly, demonstrated that interferon treatment had obvious merit in patients who were heavily pretreated and refractory to multiple chemotherapeutic regimens. Quesada et al[93] were among the first to document the effects of rHuIFN-α in non-Hodgkin's lymphoma patients; in their clinical study, 17 patients with nodular poorly differentiated lymphocytic lymphoma who had received prior treatment were given sequentially escalating doses of from 3 MU to 50 MU via intramuscular injection on a daily basis for 8 weeks. Among the patients so treated, two exhibited CRs and four exhibited partial responses (PRs). The CRs lasted for 6 and 10 months, whereas the PRs lasted for 2, 4, 10, and 12 months. Thus the study provided clear documentation of the efficacy of rHuIFN-α in nodular poorly differentiated lymphocytic lymphoma.

Other clinical trials were carried out with single-agent rHuIFN-α.[94–98] Collectively among these studies, between 30% and 50% of patients with low-grade non-Hodgkin's lymphoma exhibited an

objective clinical remission, with response rates slightly higher among previously untreated patients. Approximately 8% of all patients treated achieved a CR. Of particular note, Foon et al[95] demonstrated that clinical responses to recombinant human interferon alfa-2a (rHuIFN-α2a) therapy could be obtained in patients with previous extensive treatment. This suggested that rHuIFN-α2a is a non–cross-resistant agent with chemotherapy drugs. O'Connell et al[97] evaluated the response to rHuIFN-α2a treatment in low-grade non-Hodgkin's lymphoma patients who were previously untreated. Among the nine patients with nodular poorly differentiated lymphocytic lymphoma, four responses were obtained, including one CR, demonstrating clear antitumor activity utilizing an rHuIFN-α2a dose that was only 25% of the maximum tolerated dose in the study. Notwithstanding the high clinical response rates associated with rHuIFN-α2a as single therapy, investigators generally feel that rHuIFN-α2a alone does not represent optimal therapy in the indolent non-Hodgkin's lymphomas because it is not curative. Accordingly, most recent clinical trials have focused on interferons in combination with chemotherapeutic agents.

The pharmacologic rationale for combination therapy with rHuIFN-α and chemotherapeutic agents constitutes three elements: first, the chemotherapeutic agent's individual anticancer activity; second, the seemingly distinct cellular mechanisms of action of the agents; and third, the lack of similar clinical toxicity profiles. The biologic rationale for the combination of rHuIFN-α and chemotherapeutic agents sprang from animal model studies as well as human tumor model systems in which rHuIFN-α was combined with cyclophosphamide[99] or doxorubicin.[100] In these studies, when rHuIFN-α was administered following cytotoxic agent-induced remission, prolonged survival was noted.

Recombinant interferon combined with chemotherapeutics. The feasibility of combining a chemotherapeutic agent with rHuIFN-α was demonstrated in an early study by Hawkins et al.[101] They conducted a phase I study of rHuIFN-α2a in combination with a COPA regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone). The study included 19 patients with a variety of malignant diseases, including lymphoma. This clinical trial was intended to determine the maximum dose of rHuIFN-α2a that could be administered during midcycle while not incurring a delay in the initiation of the subsequent chemotherapeutic regimen. Patients were entered into the trial at three separate rHuIFN-α2a dose levels ranging from 2 MU/m^2 to 12 MU/m^2. The rHuIFN-α2a was administered during the last quarter of the 21-day chemotherapy cycle. The authors noted that at the highest dose level of rHuIFN-α2a, the next cycle of COPA therapy had to be delayed in six of 10 cycles because of significant neutropenia. Other than for an increase in the frequency of anemia noted in patients receiving the combination, compared with historical controls receiving COPA alone, there were no reports of unanticipated toxicity. Overall, the results of this trial provided clinical support for previous observations on the potential benefit of rHuIFN-α2a in combination chemotherapy in animal models. Nonetheless, the work of Hawkins et al[101] could not be perceived as definitive because of the broad range of malignancies in patients enrolled in the clinical trial as well as the small sample size and nominal number of dose levels administered.

Combination trials of rHuIFN-α and chemotherapeutics subsequent to the phase I and II studies described above typically employed chlorambucil or cyclophosphamide.[102–105] The study by Rohatiner et al[104] on administration of chlorambucil and recombinant human interferon alfa-2b (rHuIFN-α2b) to patients with recurrent low-grade non-Hodgkin's lymphoma clearly demonstrated that the use of this combination was clinically feasible; moreover, it provided clinical efficacy in previously treated patients. Clinical responses to therapy were observed in 14 of 23 patients enrolled in the trial; thirteen of these were PRs. In another study, Chisesi et al[103] treated 70 patients with low-grade non-Hodgkin's lymphoma. The patients received either chlorambucil (10 mg/day) or chlorambucil plus rHuIFN-α2b (5 MU/m^2 subcutaneously three times per week). A total of 63 patients were assessable for clinical response, and the study showed that similar response rates (62.1% and 64.7%, respectively) were recorded for the two treatment arms. More specifically, the patients were randomly assigned to either chlorambucil (10 mg/day for 3 weeks, followed by 1 week of rest, then resumption of chlorambucil for six additional cycles) or chlorambucil at 5 mg/day according to the same schedule in combination with rHuIFN-α2b administered at 5 MU three times weekly. Those

patients who achieved a good PR or a CR were then randomized to either no additional treatment or to 2 MU/m^2 rHuIFN-α2b for 3 weeks per month for a duration of 6 months. Again, the clinical response rates were similar between the two arms, and there was no significant difference in the duration of response. The authors cite that in patients who did respond, the clinical effects were slow but progressive, and toxicity did not increase with cumulative doses. The authors noted that, comparing patients randomized to maintenance rHuIFN-α2b vs those randomized to no further treatment, there was a decrease in the relapse rate in the maintenance arm compared with the no-treatment arm. This study would have benefited from a larger number of enrolled patients and a longer observation period; however, it does provide the suggestion that low-dose maintenance rHuIFN-α might help to delay relapse in chemotherapy-treated patients with histologically confirmed low-grade non-Hodgkin's lymphoma.

Price et al[106] have reported their preliminary analysis of the results of a clinical trial carried out at St. Bartholomew's Hospital in London. This clinical study involved randomization of patients to chlorambucil alone or chlorambucil and rHuIFN-α2b as primary therapy for stage III or IV follicular lymphoma. Patients in this trial who exhibited a response to induction therapy were then rerandomized to either maintenance rHuIFN-α2b therapy or no maintenance therapy at all. Of 124 treated patients, 108 were assessable for clinical response, with a median follow-up period of 30 months. The authors noted that myelosuppression was the major toxic side effect and was more frequent with the combination of rHuIFN-α2b and chlorambucil than it was with chlorambucil alone. During the entire study, there was no treatment-related mortality, nor was there a statistically significant difference in clinical response rates according to initial therapy. Of particular interest, among the 60 patients who exhibited a good response to initial therapy and entered the second phase of the trial, the authors report a significant prolongation of the remission period as a result of maintenance rHuIFN-α2b. The duration of response was shortest in patients who had never received rHuIFN-α2b, and the fewest relapses were reported for those patients who received rHuIFN-α2b throughout the study. Based on this preliminary analysis, the authors concluded that maintenance rHuIFN-α2b may extend the duration of remission in patients with follicular lymphoma; however, at the time of the report, no difference in survival between treatment groups was noticeable. The authors appropriately cite that additional questions remain regarding the optimal dose and duration of administration of maintenance rHuIFN-α2b in this disease.

The European Organization for Research and Treatment of Cancer has published its preliminary findings on 231 patients who responded to induction CVP chemotherapy.[107] The patients were randomized to receive either maintenance rHuIFN-α2a (3 MU/m^2 thrice weekly) or no maintenance rHuIFN-α2a. The progression-free survival of those patients who received rHuIFN-α2a maintenance was 135 weeks compared with 86 weeks for those patients who did not receive maintenance therapy. This was a statistically significant effect, although the authors also note that there was no difference in survival between treatment groups at the time of publication of their preliminary report.[107] The rHuIFN-α2a maintenance treatment in this study was very well tolerated, with only eight patients having to stop treatment because of adverse reactions to the rHuIFN-α2a.

Several additional studies of combination therapy in patients with indolent non-Hodgkin's lymphoma are noteworthy. The first study[108] was conducted at the University of Texas M. D. Anderson Cancer Center (Houston) and reported 127 patients who had presented with stage IV low-grade non-Hodgkin's lymphoma. These previously untreated patients were treated with cyclophosphamide, doxorubicin, vincristine, prednisone and bleomycin (CHOP-Bleo) for 9 to 18 months (median 13 months), followed by thrice weekly recombinant human interferon alfa-n1 (rHuIFN-αn1) (3 MU/m^2) for 24 months for those patients who had a CR. The authors report an overall response rate for the entire treatment program (including addition of radiotherapy to residual lymph node masses) of 73% CRs and 23% PRs. The 5-year survival for all 127 patients in their study was 74%. Among the group of 109 patients with follicular histology, the 5-year survival of 73% did not significantly differ from the 63% 5-year survival of the historical control group without rHuIFN-αn1. The overall failure-free survival at 5 years of the study group was 47%, and the failure-free survival at 5 years of CRs was 60%. The authors note that, compared with the findings in a group of patients with similar pretreatment clinical

features treated with CHOP-Bleo, these findings represent a significant improvement for both failure-free survival overall as well as the failure-free survival of CRs. They conclude that the combination of rHuIFN-αn1 and conventional chemotherapy with a CHOP-Bleo regimen is feasible and clinically effective. They state that maintenance rHuIFN-αn1 prolongs remission duration for patients with stage IV low-grade lymphoma. However, while these data appear relatively straightforward, Coiffier[109] appropriately addresses significant drawbacks of this study—for example, not all the patients had follicular lymphoma, and even fewer required treatment at the time of trial enrollment due to the absence of adverse prognostic factors.

The report from the Multicenter Cooperative Groupe d'Etude des Lymphomes de l'Adulte (GELA)[110] is particularly noteworthy. Their study was an open-label phase III clinical trial with 31 participating medical centers in Europe. The study evaluated the potential merit of combining rHuIFN-α2b with a regimen containing doxorubicin in a homogeneous group of patients with established follicular non-Hodgkin's lymphoma and accompanying large tumor burden. More specifically, the study involved 242 previously untreated patients with advanced low-grade follicular disease who were then treated with a regimen consisting of cyclophosphamide, doxorubicin, teniposide, and prednisone (CHVP) administered monthly for six cycles and then bimonthly for an additional 12 months. Following randomization, 119 patients received this dose-reduced CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like regimen only, while 123 patients received the chemotherapeutic regimen plus 5 MU rHuIFN-α2b thrice weekly for 18 months. The results of this study showed that the patients who were administered a chemotherapeutic agent plus rHuIFN-α2b had a significantly higher overall rate of response (85% vs 69%), a longer median event-free survival (34 months vs 19 months), and a higher rate of survival at 3 years (86% vs 69%). The CR rate was less than that reported in previous trials of chemotherapy in the non-Hodgkin's lymphomas, presumably because of the uniformly high tumor burden and/or the diminished dose-intensity of the chemotherapeutic regimen employed. Nonetheless, this is an important trial and effectively represents the first report of increased overall survival in favor of rHuIFN-α2b in a prospective randomized clinical trial. Importantly, no treatment-related deaths were reported, and 71% of patients tolerated the combination therapy with rHuIFN-α2b well, receiving treatment as scheduled. Recombinant human interferon alfa-2b administration had to be discontinued because of reversible toxicity in approximately 11% of the patients. Finally, the authors suggest that the treatment regimen employed in this study should be compared with new and promising drugs such as fludarabine and 2-chlorodeoxyadenosine.

The Eastern Cooperative Oncology Group (ECOG) conducted a study[111] to evaluate the effects of adding rHuIFN-α2a to cytotoxic chemotherapy as induction treatment in patients with clinically aggressive low-grade non-Hodgkin's lymphoma with a poor prognosis, and in certain histologic variants of intermediate-grade non-Hodgkin's lymphoma, excluding patients with diffuse histiocytic lymphoma. In this prospective randomized clinical trial, the cytotoxic chemotherapeutic regimen was COPA. The patients were randomly assigned to the COPA regimen or a combination of COPA and rHuIFN-α2a (I-COPA). Patients were to receive eight cycles of treatment, and those exhibiting a PR or a CR during either cycle seven or eight were to receive two additional cycles. Following completion of the treatment period, the patients were evaluated every 2 to 4 months for relapse. The results of this ECOG cooperative trial demonstrated an overall response rate of 86% for the COPA regimen with and without rHuIFN-α2a. Thus the two treatment regimens produced comparable objective clinical responses. However, the I-COPA regimen was associated with a prolongation of the time to treatment failure and the duration of CR. The authors indicate that addition of rHuIFN-α2a to the COPA regimen provided an increased overall survival when the results were adjusted for "important covariates."[111] They conclude that the addition of rHuIFN-α to the COPA chemotherapeutic regimen provided effective antitumor activity in patients with clinically aggressive low- or intermediate-grade non-Hodgkin's lymphoma.

The CR rate in the ECOG study (32% for I-COPA) was actually lower than that obtained in previously published studies[111] of cytotoxic chemotherapy for indolent non-Hodgkin's lymphoma. A possible explanation for this is that many of the patients had a poor prognosis due to the presence of B symptoms (fever, night sweats, and weight loss) and bulky disease; also, some had intermediate-

grade disease. In a follow-up report,[112] Andersen and Smalley indicate that at the 5-year treatment point, 81% of the patients assigned to the COPA regimen and 66% of those assigned to the I-COPA regimen had disease progression and that time to treatment failure continued to be significantly prolonged by the addition of rHuIFN-α2a. The overall survival advantage initially reported,[111] however, diminished on extended follow-up, and although the patients in the I-COPA group lived slightly longer than did those in the group without interferon treatment, follow-up disclosed no statistically significant difference between the survival curves in the two treatment groups. It was concluded at the 5-year point that addition of interferon to induction therapy for low- or intermediate-grade non-Hodgkin's lymphoma does prolong the time to treatment failure; however, it does not provide a significant improvement in the median 3- or 5-year survivals.

An intergroup trial that compared cyclophosphamide and cyclophosphamide plus rHuIFN-α2b in patients with follicular low-grade lymphomas included 581 patients enrolled over approximately 4 years.[113] Of these, 474 eligible patients with previously untreated low-grade stage III or IV follicular, small cleaved-cell, and follicular mixed lymphoma were randomized to induction therapy with cyclophosphamide or cyclophosphamide plus rHuIFN-α2b. Treatment was administered for 3 months following documentation of maximum clinical response (PR or CR). The clinical trial was later amended to incorporate (for responders) an additional randomization to either 2 years of maintenance rHuIFN-α2b or no additional treatment. The median follow-up time was 2.7 years. The preliminary data disclosed no significant difference in the overall response, survival, or time to treatment failure between the groups. The combination of cyclophosphamide and rHuIFN-α2b consistently exhibited greater toxicity than did cyclophosphamide alone. Granulocyte counts < 1000 cells/mL occurred in 29% of patients treated with cyclophosphamide and in 57% of patients who received the combination therapy. Moreover, severe infections were reported to occur at twice the rate in the combined therapy group, and fever, neurotoxicity, thrombocytopenia, and other side effects were significantly more common with the combination treatment. Adding rHuIFN-α2b to standard cyclophosphamide for induction therapy in patients with follicular low-grade lymphomas had no substantial clinical benefit; in fact, the combination appeared to result only in increased toxicity.

A strict comparison of the GELA, ECOG, and CALGB (Cancer and Leukemia Group B) clinical trials is complicated by the heterogeneity in trial design. Collectively, more than 1200 assessable patients participated in the studies of rHuIFN-α as a component of induction therapy with an established chemotherapeutic regimen for patients with low-grade non-Hodgkin's lymphoma. In these studies, the extent of tumor burden varied, and previous treatment had been received by patients in the CALGB studies but not in the other two studies. Follow-up periods also varied from 2.7 years (CALGB) to 5.2 years (ECOG), the chemotherapeutic regimens were not identical in the three studies, and the rHuIFN-α doses varied considerably. Notwithstanding the heterogeneity of design among the three trials, however, at doses of 2 to 3 MU/m^2 three times per week, rHuIFN-α was generally well tolerated, although its addition to chemotherapy did increase toxicity. Addition of rHuIFN-α to standard chemotherapeutic regimens in the treatment of follicular lymphoma is not curative, but it is associated with a prolongation of the time to treatment failure, although maximum tumor debulking helps achieve optimal results.

Interferon alfa does appear to have a significant role in maintenance therapy for patients with low-grade non-Hodgkin's lymphoma, as reported by Price et al[106] and Hagenbeek et al.[107] There is no definitive evidence that rHuIFN-α provides cure for patients with low-grade non-Hodgkin's lymphoma, but prolongation of the time to treatment failure is accomplished. These studies indicate that the majority of patients tolerate rHuIFN-α at doses of between 2 and 3 MU/m^2 three times per week. For those patients with low-grade non-Hodgkin's lymphoma who do not suffer from toxicity associated with interferon therapy, therefore, the addition of rHuIFN-α to the therapeutic armamentarium does seem reasonable.

New chemotherapeutic agents

Although the indolent B-cell non-Hodgkin's lymphomas are generally responsive to chemotherapy, with between 30% and 80% of previously untreated patients achieving PR or CR to therapy, they are fatal diseases. The median survival for low-grade non-Hodgkin's lymphoma is 7 to 10 years.[114] Most patients with these diseases will experience relapses

and will die of either an infectious complication secondary to the disease or its treatment. The impact of conventional chemotherapy, radiation therapy, or biologic agents on the low-grade lymphomas is limited by tumor-cell resistance. Although escalation of chemotherapeutic dose or radiation may in some cases overcome tumor-cell resistance, treatment-related toxicity may be unacceptable, particularly because the median age of patients at the time of diagnosis of an indolent lymphoma is greater than 50 years, and many of these patients are unwilling to accept aggressive therapy. It is now appreciated that, in many patients who achieve a "complete remission," highly sensitive laboratory techniques can detect minimal residual disease. Accordingly, although the initial clinical responses to treatment typically last for several years, virtually all patients will ultimately relapse, and such relapses are associated with a poor prognosis. New approaches to the treatment of the indolent non-Hodgkin's lymphomas must be found. Combination therapy involving chemotherapeutic agents and rHuIFN-α is encouraging, but additional studies on such combinations are required to determine effects on overall survival. In the interim, much of the commercial focus on the development of new pharmaceutical agents for the treatment of these diseases has been directed toward developing analogues of existing drugs with enhanced pharmacologic activity, such as modifications of anthracyclines and alkylating agents. Several promising agents with apparently novel mechanisms of action have recently been studied: fludarabine, 2′-deoxycoformycin (pentostatin), and 2-chlorodeoxyadenosine (cladribine).

Fludarabine. Fludarabine monophosphate is an adenine nucleoside that may have considerable value in treating the indolent non-Hodgkin's lymphomas. It has been shown to possess activity in multiple animal tumor systems, including CD8S, mammary adenocarcinoma, P388 leukemia, L1210 leukemia, and human LX-1 lung tumor xenograft.[115] Following intravenous administration, fludarabine is rapidly dephosphorylated in plasma to form 2-fluoro-arabinofuranosyl-adenine (2-F-ara-A). This dephosphorylated intermediate enters cells via both high- and low-affinity transport systems, where it is subsequently phosphorylated by the enzyme deoxycytidine kinase to fluoro-arabinofuranosyl-adenosine triphosphate (F-ara-ATP). The F-ara-ATP is incorporated into DNA and inhibits DNA synthesis as well as a variety of enzymes that have roles in DNA synthesis and repair, including DNA polymerase alpha, DNA ligase I, and ribonuclease reductase. F-ara-A nucleotides are also incorporated into RNA. It is possible that fludarabine incorporation into RNA represents a possible mechanism of action of fludarabine in the indolent non-Hodgkin's lymphomas whereby a comparatively smaller proportion of cells are present in S phase. Other mechanisms of action may be involved to explain the effects of fludarabine in the non-Hodgkin's lymphomas as well as other hematologic malignancies.[116]

Whelan et al[117] administered fludarabine as single-agent therapy to 34 patients with low-grade lymphoma and reported that, among these previously treated patients, there were six complete and seven partial responses to fludarabine—an overall response rate of 38%. The ECOG study reported by Hochster et al[118] described the results of fludarabine administration to 62 assessable patients with relapsed and refractory non-Hodgkin's lymphoma, 27 of whom had low-grade histologic features. The overall response rate was approximately 52%. The principal toxicity associated with fludarabine administration was myelosuppression. Only six of the total 62 assessable patients exhibited grade III or IV myelotoxicity in any treatment cycle; however, six patients also exhibited grade III neurotoxicity. In their phase II trial of fludarabine, Redman et al[119] treated 38 patients with low-grade non-Hodgkin's lymphoma with fludarabine at a dose slightly higher on a daily basis than that administered during the ECOG study.[118] The overall response rate reported by Redman et al[119] was approximately 55% among patients with low-grade non-Hodgkin's lymphoma. Seven of the 38 patients experienced sufficient myelosuppression (after a median treatment duration of five courses) to discontinue fludarabine therapy, although, among these patients, five had previous bone marrow involvement. There was no evidence of neurotoxicity in this trial.

Taken as a group, the phase I and II studies conducted to date suggest that fludarabine is a significant new agent in the management of low-grade non-Hodgkin's lymphoma. Overall response rates are encouraging, even though myelosuppression encountered even at low doses is a common problem. Fludarabine is immunosuppressive, and its use has been associated with an increased risk of infection.[120] Approximately one in five patients receiving fludarabine exhibits some sign of neurotoxicity,

which is typically mild and reversible. The lack of activity of fludarabine in intermediate- and high-grade lymphoma is somewhat surprising in view of the diversity of key cellular proliferation enzymes that appear to be affected by fludarabine. A recent report from Italy,[121] however, suggests that maintenance rHuIFN-α may prolong remissions after treatment with fludarabine in patients with low-grade non-Hodgkin's lymphoma.

2′-Deoxycoformycin. Pentostatin, or 2′-deoxycoformycin (DCF), is a natural product isolated from *Streptomyces antibioticus*. It closely resembles hypoxanthine and is a structural analogue of the purine adenosine; it is also structurally related to fludarabine and 2-chlorodeoxyadenosine.[122] 2′-Deoxycoformycin is a very potent, irreversible inhibitor of adenosine deaminase (ADA), which catalyzes the irreversible deamination of adenosine and deoxyadenosine to form inosine and deoxyadenosine in the purine salvage pathway. Adenosine deaminase is widely distributed in mammalian tissue with particularly high levels in T and B lymphocytes. Children congenitally deficient in ADA exhibit serious defects in lymphocyte function, manifested as a severe combined immunodeficiency syndrome. The association of this enzyme deficiency with defective lymphocyte function led to the development of DCF and related compounds as immunosuppressive and lymphocytotoxic drugs.[122] Apparently most of the biochemical effects of DCF that are consequences of ADA inhibition are more germane to proliferating cells, leaving the mechanistic basis of DCF in the indolent lymphomas uncertain. 2′-Deoxycoformycin has a variety of actions within the cell, including the inhibition of messenger RNA synthesis for interleukin-2. It is likely that multiple cell regulatory effects associated with DCF form the basis of its antineoplastic activity.

The first cooperative group study demonstrating activity of DCF in patients with lymphoma was a CALGB phase II trial reported by Duggen et al.[123] The efficacy of single-agent DCF in this study was relatively low (CR plus PR = 29%); however, toxicity was acceptable and there was no treatment-related mortality reported. Shortly after, Cummins et al[124] reported on their phase II trial of DCF in refractory lymphoma and CTCL. This ECOG study involved the treatment of 22 relapsed and refractory patients with various histologic pictures of non-Hodgkin's lymphoma. The DCF dose administered was 5 mg/m^2/day for 3 days every 3 weeks; the study reported two PRs in the 12-patient group with the low-grade histology, approximately a 17% overall response rate.

To date there have been CRs in 8% and PRs in 20% of patients treated with DCF for low-grade non-Hodgkin's lymphoma, with a median duration of 6 months. Myelosuppression with grade IV neutropenia has been seen in 5%, and grade IV thrombocytopenia has been seen in approximately 14% of DCF-treated patients. Activity of DCF in previously untreated patients with low-grade non-Hodgkin's lymphoma is undefined. In general, DCF has considerably greater activity in hairy cell leukemia than in the non-Hodgkin's lymphomas.

2-Chlorodeoxyadenosine. The molecular structure of cladribine, or 2-chlorodeoxyadenosine (2-CdA), is identical to that of deoxyadenosine with the exception of the substitution of a chlorine atom for a hydrogen atom at position 2 of the purine ring of deoxyadenosine, the natural substrate for ADA.[125] The cellular mechanism of action of 2-CdA is not well understood, although it is believed to cause DNA strand breaks that in turn activate poly(adenosine diphosphate-ribose) polymerase, resulting in depletion of nicotinamide adenine dinucleotide, with accompanying cell death. The enzyme deoxycytidine kinase catalyzes the intracellular phosphorylation of 2-CdA to 2-chlorodeoxyadenosine triphosphate, which is known to inhibit DNA synthesis in replicating cells and is also cytotoxic to lymphocytes and monocytes.[126,127] Evidence suggests[128] that 2-CdA is cytotoxic to nonreplicating cells by triggering programmed cell death (apoptosis) in malignant lymphocytes.[128]

Clinical experience with 2-CdA in the treatment of patients with low-grade non-Hodgkin's lymphoma is limited. Kay et al[129] reported results in 40 patients who had failed a median of three prior standard chemotherapeutic regimens; 20% achieved a CR, and 23% a PR. The median response duration was approximately 5 months; however, among the eight patients achieving a CR, four remained in continuous CR at 2, 12, 29, and 33 months. The overall response rate (43%) is encouraging. However, side effects were relatively common, with grade III to IV thrombocytopenia in 30% and grade III to IV neutropenia in 18% of patients. In patients with intermediate- and high-grade non-Hodgkin's lymphoma,[130] combinations of 2-CdA with various chemotherapeutic agents may result in improved clinical response rates.

Stage I or II aggressive lymphoma

According to the Working Formulation,[7] the intermediate-grade lymphomas comprise four diseases: follicular predominantly large-cell, diffuse small cleaved-cell, diffuse mixed small- and large-cell, and diffuse large-cell lymphomas. Although immunoblastic lymphoma is categorized in the Working Formulation as a high-grade neoplasm, it is commonly treated as an intermediate-grade tumor. These five diseases have many clinical characteristics in common. Follicular predominantly large-cell tumors behave clinically in a fashion similar to that of the diffuse large-cell lymphomas. Many follicular predominantly large-cell tumors undergo conversion to diffuse large-cell lymphomas in the absence of curative treatment. Diffuse small cleaved-cell lymphomas are problematic for a variety of reasons, including the fact that many patients presenting with this form of lymphoma are elderly and commonly exhibit stage IV disease at initial presentation; it is not unusual for such patients to present with extensive bone marrow, liver, spleen, and pulmonary tumor infiltration. The diffuse mixed small- and large-cell variety of intermediate-grade non-Hodgkin's lymphoma behaves similarly to the diffuse large-cell lymphomas and commonly involves elderly women, who present with extranodal disease involvement of the gastrointestinal tract and skin. The most commonly encountered intermediate-grade lymphoma is the diffuse large-cell variety, a particularly invasive form of lymphoma that may produce compression of major blood vessels and airways. Patients typically present with enlarged cervical lymph nodes or prominent extranodal disease in the gastrointestinal tract, skin, bone, brain, and other organs. At initial presentation, tumor infiltration of bone marrow occurs in less than 20% of patients; however, its presence is an omen of disease spread to the central nervous system (CNS). Accordingly, spinal fluid analysis is important in patients with bone marrow infiltration.

A wide variety of multiagent chemotherapeutic regimens are available for treatment of intermediate-grade lymphomas.[59,131] Little evidence suggests that any chemotherapeutic regimen is superior to the others. The CHOP regimen is the most widely used in the treatment of diffuse large-cell non-Hodgkin's lymphoma. Long-term follow-up data from the Southwest Oncology Group (SWOG) for several studies employing the CHOP regimen disclosed a complete remission rate of more than 50%, with approximately 30% of all treated patients experiencing a sustained CR.[3,132]

As mentioned above, there is no universally accepted treatment regimen for intermediate-grade non-Hodgkin's lymphomas. Many patients with stage I or II disease have microscopic spread of the disease to distant sites; therefore, combination chemotherapy is considered standard treatment. Patients who present with regional disease may benefit from combination chemotherapy (eg, CHOP) and regional radiotherapy. It is not known, however, whether regional radiation therapy is a necessary adjuvant to multiagent chemotherapy in stage I or II disease. In the nonrandomized study reported by Jones et al,[133] 8 of 34 patients (24%) treated with a CHOP regimen alone relapsed, compared with 15 of 108 patients (14%) who received CHOP followed by local radiation therapy. Mauch et al[134] in a retrospective study reported improved survival following combined chemotherapy and radiation therapy in patients with stage I-II non-Hodgkin's lymphoma. The authors reported a lower freedom-from-progression rate (43% vs 66%) and survival rate (56% vs 80%) in patients treated only with chemotherapy. This was the case even when patient subgroups were stratified according to histology, disease stage, and chemotherapy. By contrast, other studies[135,136] do not disclose a substantial advantage of radiation therapy to previously involved sites.

Tondini et al[137] provide encouraging data on the combination of primary CHOP chemotherapy followed by local irradiation of patients with stage I and II histologically aggressive lesions. This single-center, prospective, nonrandomized clinical study involved 183 patients with stage I or II nodal and extranodal lymphomas with no more than three sites of disease involvement. Treatment included four cycles of CHOP chemotherapy (six cycles in partial responders). Radiation therapy to initial sites of disease involvement and to proximal uninvolved nodal regions was administered promptly following completion of administration of the chemotherapeutic regimen. The authors reported a CR rate of 98% at the end of the combined therapy. After a median follow-up period of more than 4 years, 26 patients had relapsed and 25 had died. The 5-year relapse-free and total survival rates were 83%. With the exception of age greater than 60 years, other factors, including disease stage, histology, presence of extranodal lesions, bulky lymphoma, or elevated LDH, were

not predictive of treatment outcome. The authors reported a trend toward higher relapse rates for patients achieving CR at the time of radiation therapy (31%) compared with those achieving CR with chemotherapy (15%) or with initial surgery (10%). They also mentioned that the treatment was well tolerated, with no deaths due to acute toxicity. They concluded that patients who present with limited-stage aggressive non-Hodgkin's lymphomas may be safely and effectively treated with a short course of CHOP followed by local radiation therapy; this approach is curative for most such patients and should be regarded as standard therapy for these patients. Although these studies do not provide evidence of the definitive effects of adjuvant radiotherapy following effective chemotherapy for patients with early-stage histologically aggressive non-Hodgkin's lymphoma, randomized clinical trials are in progress to clarify the impact of combined chemotherapy and radiation therapy.

Stage III or IV aggressive lymphoma

The treatment of choice for all patients with stage III or IV intermediate-grade non-Hodgkin's lymphoma is combination chemotherapy. The first-generation chemotherapeutic regimens, developed between 1965 and 1975, typically included four or five chemotherapeutic agents. Their administration resulted in CRs in 45% to 55% of patients and achieved cure in approximately 30% to 35%.[42,138–140] These regimens include CHOP, BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone), C-MOPP, and COMLA (cyclophosphamide, vincristine, methotrexate with leucovorin rescue, and cytarabine). Of these, CHOP emerged as standard therapy for patients with advanced-stage intermediate- or high-grade non-Hodgkin's lymphoma. During the late 1970s and early-to-mid 1980s, oncologists and hematologists attempted to improve the CR and cure rates in these diseases by administration of more intensive chemotherapeutic regimens incorporating between six and eight separate drugs. These second- and third-generation regimens include ProMACE-CytaBOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue), ProMACE-MOPP (prednisone, methotrexate, doxorubicin, cyclophosphamide, and etoposide alternating with nitrogen mustard, vincristine, procarbazine, and prednisone), MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), and m-BACOD (methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone). Some commonly used chemotherapeutic regimens, their typical doses, routes, and administration schedules are presented in *Table 5*. As a group, these chemotherapy programs were associated with approximately 70% to 75% CR rates and approximately 50% long-term survival rates.[131] Unfortunately, these regimens were also commonly associated with greater toxicity, particularly bone marrow depression and severe mucositis. In addition, the cost of these treatment regimens is substantial.

Reports from several large lymphoma-referral centers in the United States indicated that use of second- and third-generation chemotherapeutic regimens was accompanied by CR rates of up to 85% and predicted long-term survival rates as high as 65%.[131] Despite enthusiasm, there was concern that these pilot studies overestimated the relative merit of the second- and third-generation regimens. Some of the studies involved comparison of their clinical results with historical data from large cooperative group studies despite the fact that the study populations were heterogeneous. Also, some of the studies at single institutions involved short follow-up periods; more extensive follow-up disclosed a substantial increase in late relapses as well as deaths.

To conduct a valid comparison of these chemotherapeutic regimens, the SWOG initiated a prospective randomized phase III clinical trial comparing CHOP, m-BACOD, ProMACE-CytaBOM, and MACOP-B regimens for the treatment of patients with intermediate-grade or high-grade non-Hodgkin's lymphoma.[141] Approximately 2 years after study initiation, the ECOG joined the study, designated the National High-Priority Lymphoma Study.[141] The end points of this clinical trial were response rate, time to treatment failure, overall survival, and incidence of severe or life-threatening toxicity. A total of 1138 patients registered for this clinical trial, of whom 899 were determined to be eligible; each treatment group contained at least 218 patients. Randomization was stratified according to several factors, including the presence of bone marrow infiltration or bulky disease, LDH levels above or below 250 U/L, age (< 65 vs ≥ 65 years), and Working Formulation group. The results of this

TABLE 5
CHEMOTHERAPEUTIC REGIMENS*

Regimen	Dose and route†	Day	Frequency
CVP			Every 21 days
C: Cyclophosphamide	400 mg/m^2 PO	1–5	
V: Vincristine	1.4 mg/m^2	1	
P: Prednisone	100 mg/m^2 PO	1–5	
C-MOPP			Every 28 days
C: Cyclophosphamide	650 mg/m^2 IV	1, 8 days	
O: Vincristine	1.4 mg/m^2 IV	1, 8	
P: Procarbazine	100 mg/m^2 PO	1–14	
P: Prednisone	40 mg/m^2 PO	1–14	
BACOP			Every 28 days
B: Bleomycin	5 mg/m^2 IV	15, 22	
A: Doxorubicin	25 mg/m^2 IV	1, 8	
C: Cyclophosphamide	650 mg/m^2 IV	1, 8	
O: Vincristine	1.4 mg/m^2 IV	1, 8	
P: Prednisone	60 mg/m^2 PO	15–28	
CHOP			Every 21 days
C: Cyclophosphamide	750 mg/m^2 IV	1	
H: Doxorubicin	50 mg/m^2 IV	1	
O: Vincristine	1.4 mg/m^2 IV (maximum 2.0 mg)	1	
P: Prednisone	100 mg PO	1–5	
COMLA			Every 91 days
C: Cyclophosphamide	1500 mg/m^2 IV	1	
O: Vincristine	1.4 mg/m^2 IV (maximum 2.0 mg)	1, 8, 15	
M: Methotrexate‡	120 mg/m^2 IV	36, 43, 50, 57, 64, 71	
L: Leucovorin	25 mg/m^2 PO × 4	24 hours after methotrexate	
A: Cytarabine	300 mg/m^2	Same as methorexate	
COP/BLAM			Every 21 days
C: Cyclophosphamide	400 mg/m^2 IV	1	
O: Vincristine	1 mg/m^2 IV	1	
P: Prednisone	40 mg/m^2 PO	1–10	
BL: Bleomycin	15 mg/m^2 IV	15	
A: Doxorubicin	40 mg/m^2 IV	1	
M: Procarbazine	100 mg/m^2 PO	1–10	
M-BACOD			Every 21 days
M: Methotrexate‡	3000 mg/m^2 IV	15	
B: Bleomycin	4 mg/m^2 IV	1	
A: Doxorubicin	45 mg/m^2 IV	1	
C: Cyclophosphamide	600 mg/m^2 IV	1	
O: Vincristine	1 mg/m^2 IV	1	
D: Dexamethasone	6 mg/m^2 PO	1–5	
m-BACOD			Every 21 days
m: Methotrexate‡	200 mg/m^2 IV	8, 15	
B: Bleomycin	4 mg/m^2 IV	1	
A: Doxorubicin	45 mg/m^2 IV	1	
C: Cyclophosphamide	600 mg/m^2 IV	1	
O: Vincristine	1.0 mg/m^2 IV	1	
D: Dexamethasone	6 mg/m^2 PO	1–5	

Continued

intergroup study demonstrated no significant difference among the treatment groups in the rates of objective antitumor responses, PRs, or CRs.[142] At 3 years, 44% of all patients enrolled in the trial were alive without disease (41% for CHOP and MACOP-B, 46% for m-BACOD and ProMACE-CytaBOM regimens). Overall survival for the entire group at 3 years was 52% (ProMACE-CytaBOM and MACOP-B were 50%, CHOP was 54%, and m-BACOD was 52%). There was no subgroup of patients in which survival was improved by administration of a third-generation regimen. The incidence of fatal toxic reactions was least in the CHOP group (1%). Fatal toxicity associated with admini-

TABLE 5
CHEMOTHERAPEUTIC REGIMENS* *(Continued)*

Regimen	Dose and route†	Day	Frequency
ProMACE-MOPP			Every 28 days
Pro: Prednisone	60 mg/m^2 PO	1–14	
M: Methotrexate‡	1500/m^2 IV	15	
A: Doxorubicin	25 mg/m^2 IV	1, 8	
C: Cyclophosphamide	650 mg/m^2 IV	1, 8	
E: Etoposide	120/ mg/^{2} IV	1, 8	
Followed by MOPP after maximal response			
M: Mechlorethamine	6 mg/m^2 IV	1, 8	Every 28 days
O: Vincristine	1.4 mg/m^2 IV	1, 8	
P: Procarbazine	100 mg/m^2 PO	1–14	
P: Prednisone	40 mg/m^2 PO	1–14	
ProMace-CytaBOM			Every 21 days
Pro: Prednisone	60 mg/m^2 PO	1–14	
A: Doxorubicin	25 mg/m^2 IV	1	
C: Cyclophosphamide	650 mg/m^2 IV	1	
E: Etoposide	120 mg/m^2 IV	1	
Cyta: Cytarabine	300 mg/m^2 IV	8	
B: Bleomycin	5 mg/m^2 IV	8	
O: Vincristine	1.4 mg/m^2 IV	8	
M: Methotrexate‡	120 mg/m^2 IV	8	
ProMACE d1/MOPP d8			Every 28 days
Pro: Prednisone	60 mg/m^2 PO	1–14	
M: Methotrexate‡	500 mg/m^2 IV	15	
A: Doxorubicin	25 mg/m^2 IV	1	
C: Cyclophosphamide	650 mg/m^2 IV	1	
E: Etoposide	120 mg/m^2 IV	1	
M: Mechlorethamine	6 mg/m^2 IV	8	
O: Vincristine	1.4 mg/m^2 IV	8	
P: Procarbazine	100 mg/m^2 POd	8–14	
MACOP-B			Every 84 days
M: Methotrexate‡	400 mg/m^2 IV	8, 36, 64	
A: Doxorubicin	50 mg/m^2 IV	1, 15, 29, 43, 57, 71	
C: Cyclophosphamide	350 mg/m^2 IV	1, 15, 29, 43, 57, 71	
O: Vincristine	1.4 mg/m^2 IV (maximum 2.0 mg)	8, 22, 36, 64, 78	
P: Prednisone	75 mg/m^2 PO	1–84	
B: Bleomycin	10 mg/m^2 IV	22, 50, 78	

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†IV, intravenous; PO, by mouth; POd, by mouth daily
‡Leucovorin rescue is given 24 hours after each methotrexate dose; dose duration and schedule differ in each protocol

stration of ProMACE-CytaBOM, m-BACOD, and MACOP-B was 3%, 5%, and 6%, respectively. The toxic reactions that were reported were similar to those documented in previous phase II trials of the same regimens. The most severe reactions were associated with granulocytopenia and resultant infection. There was no statistical significance between the incidence rates of fatal (grade V) toxic reactions among the treatment groups. In contrast, grade IV (life-threatening) toxic reactions were recorded in 31% of patients receiving CHOP, 29% of those receiving ProMACE-CytaBOM, 43% of those receiving MACOP-B, and 54% of those receiving m-BACOD regimens. When grades IV and V reactions were combined, statistically significant differences were found among the regimens, with CHOP and ProMACE-CytaBOM less toxic than m-BACOD and MACOP-B ($P = .01$).

The National High-Priority Lymphoma Study was designed to detect a 15% difference in treatment failure rates between CHOP and the third-generation regimens. Additional follow-up of the patients in this clinical study is unlikely to demonstrate that any of the third-generation chemotherapeutic regimens included actually reduces the treatment failure rate by 15% compared with standard CHOP therapy. The authors concluded that CHOP remains the best available treat-

ment for patients with advanced-stage intermediate- or high-grade non-Hodgkin's lymphoma.

The results of the National High-Priority Lymphoma Study indicate that approximately 55% to 65% of patients with advanced-stage intermediate- or high-grade non-Hodgkin's lymphoma will be either refractory to multiagent chemotherapeutic regimens or will relapse following initial combination chemotherapy.[141] Some patients resistant to standard chemotherapeutic or salvage regimens may achieve a complete remission when administered very high doses of chemotherapy or combined chemotherapy and radiation, although these approaches tend to be associated with profound and life-threatening myelosuppression. Alternative approaches in refractory or relapsed patients may be autologous bone marrow transplantation (ABMT) or, in applicable cases, transplantation using bone marrow obtained from an HLA-matched relative or an identical twin. Complete response or even cure is more likely among patients who exhibit a favorable response to initial combination chemotherapy and who, at the time of bone marrow transplantation, possess no residual tumor or minimal residual disease and have had a favorable response to salvage chemotherapy. Patients who exhibit progressive disease on salvage therapy prior to bone marrow transplantation are unlikely to benefit, as are patients who failed or responded poorly to initial therapy.

Bone marrow transplantation is not universally applicable to patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Patients with bone marrow involvement or of advanced age and generally poor medical condition will not be suitable candidates for transplantation. Such patients are typically administered conventional-dose salvage chemotherapy. Objective recommendation of a particular salvage regimen is difficult because of the absence of randomized, prospective clinical trials in patients with aggressive non-Hodgkin's lymphoma. Nevertheless, salvage regimens have been proposed, incorporating drugs that have for the most part not been employed in initial chemotherapy.[131] Generally speaking, approximately 20% to 35% of patients exhibiting an initial CR will achieve a second CR with salvage chemotherapy. DHAP (dexamethasone, high-dose ara-C, and cisplatin) has consistently been associated with CR rates in 15% to 30% of cases. This regimen is commonly used before bone marrow transplantation in an attempt to debulk tumor; the response to the DHAP regimen is used to identify patients with sensitive vs resistant relapse. Existing data do not indicate whether patients with resistant or relapsed aggressive lymphoma can be cured with the available salvage combination regimens. An ongoing randomized prospective multinational clinical trial[142] is studying the potential value of high-dose chemotherapy followed by bone marrow transplantation for relapsed patients responsive to conventional DHAP salvage therapy.

In patients with intermediate- or high-grade non-Hodgkin's lymphoma, prolongation of disease-free survival appears to be similar with either autologous (ABMT) or allogeneic bone marrow transplantation.[143] Because ABMT appears to be more advantageous when the procedure is carried out earlier in the course of the disease, a number of physicians are attempting to use high-dose chemotherapy combined with ABMT as primary treatment for patients with intermediate- or high-grade non-Hodgkin's lymphoma.[144–147] Data to date indicate disease-free survival of 60% to 90% at 2- or 3-year time points for patients with poor prognoses.

High-grade lymphoma

According to the Working Formulation, three diseases constitute the high-grade non-Hodgkin's lymphomas: large-cell immunoblastic, lymphoblastic, and small noncleaved-cell lymphomas. Immunoblastic lymphoma (diffuse histiocytic variety in the Rappaport Classification) is commonly treated as an intermediate-grade lesion. Lymphoblastic lymphoma represents a unique subgroup of the non-Hodgkin's lymphomas, exhibiting clinical behavior reminiscent of T-cell acute lymphocytic leukemia, manifesting early and widespread dissemination with frequent bone marrow involvement and CNS metastasis. Although lymphoblastic lymphoma and small noncleaved-cell lymphoma share a number of similar clinical characteristics, virtually all lymphoblastic lymphomas are of the T-cell variety, whereas small noncleaved-cell lymphoma is a B-cell disorder. The high-grade non-Hodgkin's lymphomas have a very poor prognosis and demand aggressive treatment, most commonly with high-dose combination chemotherapy accompanied by CNS prophylaxis. Irrespective of the particular chemotherapy regimen employed, it is important for the physician to pay particular attention to the general clinical care of the patient, renal and hepatic function, electrolyte balance, and degree of

hydration. Although drug-related toxicity will vary depending upon the selection of the chemotherapeutic regimen, the dose-limiting toxicity most commonly encountered is myelosuppression. Patients presenting at any time in their disease course with fewer than 1000 granulocytes/mm^3 and fever must be immediately hospitalized and treated with broad-spectrum antibiotics. When platelet counts drop below 20 000/mm^3, platelet transfusion is indicated.

A variety of chemotherapeutic regimens have been employed in the treatment of patients with lymphoblastic lymphoma[148–151] and small noncleaved-cell lymphoma.[152–154] The regimen described by Coleman et al[150] was associated with the highest rate of CR (95%). Their study involved induction therapy with a regimen consisting of cyclophosphamide, doxorubicin, vincristine, prednisone, and asparaginase and maintenance therapy involving methotrexate and 6-mercaptopurine. Three-year disease-free survival was 56% in patients so treated. The patients in this study also received CNS prophylaxis of intrathecal and high-dose systemic methotrexate and cranial radiotherapy. Levine et al[149] used a more complicated regimen involving, for induction, cyclophosphamide, doxorubicin, vincristine, prednisone, cytarabine, thioguanine, asparaginase, and lomustine, and, for maintenance, thioguanine, cyclophosphamide, hydroxyurea, methotrexate, lomustine, doxorubicin, cytarabine, and vincristine. Patients received CNS prophylaxis consisting of intrathecal methotrexate and cranial radiotherapy. These patients also received irradiation to the mediastinum. The rate of CR was 73%, and disease-free survival at 5 years was 35%.

The expanded chemotherapeutic regimens employed by Coleman et al[150] and Levine et al[149] in patients with lymphoblastic lymphoma represent considerable improvement over previous attempts to use CVP or CHOP-Bleo regimens, frequently in combination with radiation therapy, by which the median survival of patients was only approximately 15 months. Central nervous system prophylaxis was included in these studies because of the experience originally reported by the Stanford group (Coleman et al[150]) in their pilot series, in which 13 patients were treated and achieved CR although four of the 13 patients exhibited relapse in the CNS. In the subsequent and larger study reported by Coleman et al[150] involving 44 patients, the original protocol was modified to initiate CNS prophylaxis earlier and also to incorporate cranial radiotherapy. Their regimen, which involved induction, consolidation, and maintenance phases in addition to CNS prophylaxis with intrathecal methotrexate and cranial radiation, produced encouraging results. Of 44 patients assessable for treatment response, two achieved a PR and 42 achieved a CR. The studies[149,150] carried out to date demonstrate that leukemia-like treatment regimens that involve intensive induction, consolidation, and maintenance phases in addition to CNS prophylaxis provide considerable clinical benefit to a substantial number of patients with adult lymphoblastic lymphoma, although the need remains for novel approaches affording even better rates of CR, disease-free survival, and overall survival.

Studies evaluating various chemotherapeutic regimens for the treatment of small noncleaved-cell lymphoma have provided encouraging results.[151–153] Complete response rates have been approximately 80%, with disease-free survival rates at 1- to 5-year treatment points in the range of 60% to 70%. The regimens employed have included, among others, combinations of cyclophosphamide, vincristine, bleomycin, doxorubicin, methotrexate, etoposide, and prednisone, with or without intrathecal methotrexate as CNS prophylaxis,[154] and cyclophosphamide, doxorubicin, vincristine, prednisone, and methotrexate, including intrathecal methotrexate as CNS prophylaxis.[152] In the latter study,[152] radiation therapy was also provided to all bulky unresected masses.

When patients present with extensive infiltration of the bone marrow (> 25% blasts), it is appropriate to administer acute lymphoblastic leukemia-type chemotherapeutic regimens.[151,155,156] As mentioned, some patients with aggressive non-Hodgkin's lymphomas also experience metabolic complications—for example, elevated serum uric acid and increased serum creatinine related to tumor lysis syndrome or uric acid nephropathy. The tumor lysis syndrome is usually associated with rapid clinical responses in patients exhibiting bulky disease. Adequate hydration, alkalinization of the urine, and prophylactic allopurinol are commonly used to treat such complications. Metabolic complications during chemotherapy for aggressive lymphomas may be manifested dramatically. For instance, rapid killing of large numbers of tumor cells by chemotherapy-driven release of cellular phosphate into the circulation may cause a rapid decline

in serum calcium levels that, when coupled with elevated serum potassium levels, can result in cardiac arrest.

Dissemination of tumor to the CNS in patients with aggressive non-Hodgkin's lymphoma carries a very poor prognosis. Nonetheless, some patients will respond well to intensive combination chemotherapy and may achieve increased long-term survival.[157,158] Primary CNS non-Hodgkin's lymphoma is not frequently encountered in patients who are not immunocompromised; the accelerating AIDS epidemic will increase the frequency with which oncologists encounter primary CNS lymphoma. At present, this disorder is treated with intrathecal chemotherapy (with or without radiation), systemic intensive chemotherapy (with or without radiation), and osmotic blood-brain barrier disruption.[159–161] Addition of radiation therapy to effective chemotherapeutic regimens significantly improves the median survival in adult primary CNS lymphoma; local control and overall outcome are improved when the dose is in excess of 40 Gy to 50 Gy. A chemotherapeutic regimen that has shown promise in the treatment of such patients incorporates vincristine, doxorubicin, cyclophosphamide, and prednisolone.[159] The place of high-dose intravenous methotrexate in treatment of patients with primary CNS lymphoma appears to be rather well established.[161,162]

One of the very challenging aspects of lymphoma therapy involves treatment of patients with HIV infection who present with non-Hodgkin's lymphoma. Levine[163] has discussed the clinical and biologic characteristics as well as potential treatment approaches. Non-Hodgkin's lymphomas in HIV-infected patients are typically intermediate-grade diffuse large-cell or high-grade small noncleaved-cell tumors. Their clinical behavior and response to treatment differ considerably from that of intermediate- and high-grade non-Hodgkin's lymphomas in HIV-negative patients, despite considerable similarity in histologic features. Intensive chemotherapeutic regimens have relatively little impact; in the presence of opportunistic infection, patients exhibit poor responses to chemotherapy.[164] However, some HIV-positive patients with non-Hodgkin's lymphoma may respond to chemotherapy in the absence of opportunistic infection. At present, there is no standard chemotherapeutic regimen for treatment of these patients. In some circumstances, intense chemotherapeutic combinations are preferable, whereas in other situations a less intense regimen may offer better clinical results.[165,166]

Treatment of elderly patients

Age is an important independent prognostic factor for clinical response and survival in patients with aggressive non-Hodgkin's lymphoma.[40,167–171] Elderly patients in general have poor clinical outcomes, even when adjusted for higher rates of death from causes unrelated to the lymphoma.[172] Elderly patients with aggressive non-Hodgkin's lymphoma have prognostic factors comparable to those of younger patients. Vose et al[167] have reported that the specific causes of death in elderly patients with aggressive non-Hodgkin's lymphoma are related to progression of the disease or treatment toxicity, especially cardiovascular and infectious complications. Investigators have attempted to address the problem of treatment of elderly patients with aggressive non-Hodgkin's lymphoma by developing chemotherapeutic regimens specifically tailored for these patients.[173–177] O'Reilly et al[173] reported that elderly patients with advanced-stage diffuse large-cell lymphoma were administered weekly chemotherapy with low-dose ACOP-B (low-dose doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) and VABE (etoposide, doxorubicin, vincristine, prednisone, and bleomycin). Of 72 patients (ages 65 to 85 years) prospectively administered successive ACOP-B and VABE regimens, overall response rates ranged between approximately 70% and 90%; however, the VABE regimen was associated with grade IV hematologic toxicity in 58% of patients. The low-dose ACOP-B regimen was associated with a 28% overall survival rate at 6 years, and the VABE regimen yielded a 36% overall survival rate at 4 years.

Gaynor et al[178] have recently reported on their analysis of factors accounting for diminished survival of elderly (> 60 years) patients participating in the National High-Priority Lymphoma Study (SWOG-8516). In this randomized prospective study, patients with intermediate- and high-grade lymphoma were treated with the same initial drug dose irrespective of age. The age-adjusted risk index[40] indicated a similar risk profile for patients in the elderly as opposed to nonelderly group. Results showed that elderly patients exhibited a poorer outcome than did those age 60 or under. The incidence in each age group of fatal toxicities was similar for patients in the CHOP, m-BACOD, and ProMACE-

CytaBOM treatment arms; however, a significantly higher incidence was noted in patients assigned to the MACOP-B treatment arm. The authors concluded that the poor survival of elderly patients in this trial could be attributed to treatment with MACOP-B, although the survival of elderly patients receiving full initial doses of CHOP, m-BACOD, or ProMACE-CytaBOM was similar to that of patients age 60 or under.

TABLE 6
TREATMENT OF NON-HODGKIN'S LYMPHOMAS

Category	Option
Low-grade	
Stage I or II	Radiation
Stage III or IV	Watch and wait or combination chemotherapy ± interferon-alfa
Intermediate-grade	
Stage I or II	CHOP ± radiation
Stage II, bulky, III, IV	CHOP
High-grade	
Lymphoblastic	Combination chemotherapy + CNS prophylaxis ± radiation
Small noncleaved-cell (Burkitt's)	Combination chemotherapy

Tirelli et al[174] reported on patients older than 70 years with unfavorable non-Hodgkin's lymphoma who were treated with a chemotherapeutic regimen involving VMP (etoposide, mitoxantrone, and prednimustine). Median survival was approximately 14 months, and the percentage of patients exhibiting a clinical response was high. In most cases, the lymphoma was the cause of death.

CONCLUSIONS

At present, approximately one half of patients under 70 years of age with aggressive non-Hodgkin's lymphoma can achieve a complete remission with a chance for long-term survival and a reasonable quality of life. During the past 30 years, much has been learned about the genetics, immunology, and basic cellular biology of this diverse group of diseases. A recently developed classification system[7] has helped to clarify the disease by providing a uniform language permitting accurate diagnosis and subsequent treatment. Most of the non-Hodgkin's lymphomas are sensitive to chemotherapy and radiation therapy, but whereas some varieties are curable, others exhibit a characteristic pattern of initial clinical response followed by multiple relapses. A tabular presentation of general treatment options presented in *Table* 6 and schematically represented in the *Figure* indicates that for early-stage low-grade non-Hodgkin's lymphomas, radiation is the treatment of choice. For advanced-stage indolent lymphomas, a watch-and-wait approach may be sufficient, or combination chemotherapy incorporating rHuIFN-α may be successful. The intermediate-stage non-Hodgkin's lymphomas are treated by combination chemotherapy with or without radiation, depending upon the stage and presence or absence of bulky disease. The high-grade non-Hodgkin's lymphomas present a clinical challenge to the treating oncologist; treatment options for this category of disease include combination chemotherapy with CNS prophylaxis, possible radiation therapy, and, in some cases, autologous or allogeneic bone marrow transplantation.

It is important that an experienced pathologist be included in the morphologic and laboratory diagnosis of patients with suspected non-Hodgkin's lymphoma. In the absence of accurate diagnosis, it is unlikely that optimal treatment plans can be developed. The treating oncologist must exercise particular diligence in the physical evaluation of all patients at initial diagnosis and during their continuing care. Moreover, the oncologist and the adjuvant professional team must sufficiently educate patients about the clinical nature of their disease so that situations of great clinical concern may be rapidly identified, such as fever associated with neutropenia following combination chemotherapy.

With the availability of sophisticated laboratory techniques and through ongoing clinical trials of new agents as well as modifications of existing combination chemotherapeutic regimens, new treatments will likely be developed to improve the clinical state and extend the survival of non-Hodgkin's lymphoma patients.

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