



Venice, Italy, 1996. Courtesy of Oscar F. Ballester, MD.

*Advances in the classification,  
therapies, and treatment  
strategies for older patients  
with non-Hodgkin's lymphoma  
should lead to more effective  
management.*

# Non-Hodgkin's Lymphoma in the Elderly

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**Background:** *The incidence of non-Hodgkin's lymphoma in the elderly continues to increase. There has been a tendency among some treating physicians to minimize appropriate workup and treatment, which may produce a negative effect on outcomes.*

**Methods:** *Several characteristics of non-Hodgkin's lymphoma in the elderly are reviewed, including classification and staging, pathophysiology, clinical presentation, and treatment strategies.*

**Results:** *The Working Formulation remains the principal classification used. In older and younger individuals, the prevalence of histologic subtypes and the stage at presentation are similar. Regardless of the regimen chosen, doxorubicin or mitoxantrone should be included if optimal responses are to be obtained. New purine analogs extend the therapeutic armamentarium.*

**Conclusions:** *Advanced age and comorbidities can impair the capability for treatments to control non-Hodgkin's lymphoma. To enhance results, more studies that focus on the elderly are needed on drug combinations and the newer purine analogs.*

## Introduction

The overall incidence of non-Hodgkin's lymphoma (NHL) has been rising during the past few

decades.<sup>1,2</sup> According to the National Cancer Institute, the incidence per 100,000 persons climbed from 8.5 in 1973 to 13.7 in 1987 — an increase of more than 50%.<sup>3</sup> The increase has been largely confined to two age groups: men 24 to 54 years of age and individuals  $\geq 65$  years of age.<sup>2</sup> In fact, data from the Veterans Affairs medical system have shown that approximately half of all NHLs now occur in individuals  $\geq 60$  years of age.<sup>4</sup>

Whereas the increase in NHLs among younger men is likely the result of the spread of the acquired immunodeficiency syndrome (AIDS),<sup>5</sup> reasons for the increase among older persons remain unclear.

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Table 1. — Working Formulation for Non-Hodgkin's Lymphoma<sup>8</sup>

<b>Low grade</b>	
	Malignant lymphoma, small lymphocytic
	Malignant lymphoma, follicular, predominantly small cleaved cell
	Malignant lymphoma, follicular, mixed small cleaved cell and large cell
<b>Intermediate grade</b>	
	Malignant lymphoma, follicular, predominantly large cell
	Malignant lymphoma, diffuse small cleaved cell
	Malignant lymphoma, diffuse mixed small and large cell
	Malignant lymphoma, diffuse large cell
<b>High grade</b>	
	Malignant lymphoma, large cell immunoblastic
	Malignant lymphoma, lymphoblastic
	Malignant lymphoma, small noncleaved cell

Table 2. — Stages of Non-Hodgkin's Lymphoma<sup>10</sup>

Stage	Description
I	Involvement of one lymph node area
II	Involvement of two or more nodal areas on the same side of the diaphragm
III	Involvement of lymph nodes on both sides of the diaphragm
IV	Involvement of extranodal tissues
A = Asymptomatic disease, absence of systemic symptoms.	
B = Disease with systemic symptoms (eg, fever $\geq 101^\circ\text{F}$ for at least 1 week, loss of $\geq 10\%$ of original body weight over 6 months, night sweats causing a change in night garments).	
E = Disease with involvement of one or more extranodal areas in contiguity with involved lymph nodes.	

In view of the higher occurrence of NHL in the elderly, clinicians who treat this population must be familiar with disease classification systems, epidemiologic patterns, pathophysiologic mechanisms, clinical presentations, and conventional as well as newer treatment strategies.

## Classification and Staging of NHL

The histologic classification of NHL has been a subject of continuing discussion. Several systems are currently in use: the Kiel classification,<sup>6</sup> the Lukes-Collins classification,<sup>7</sup> and the Working Formulation.<sup>8</sup> Nomenclature, categorization of disease entities, and diagnostic criteria vary from system to system. Also, no one system encompasses all of the newer lymphoma entities that have been described over the years. The lack of consensus on lymphoma classification presents difficulties for pathologists and clinicians and confounds interpretation of published studies.<sup>9</sup> The International Lymphoma Study Group recently proposed a Revised European-American Lymphoma classification scheme in an attempt to surmount some of these obstacles.<sup>9</sup> According to the study group, the

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intention of this scheme is not to replace existing classifications but rather to summarize current knowledge in a practical format, to serve as a preliminary attempt "to bring some order to the chaos of lymphoma categorization," and to provide a framework for further study.

Even as such efforts continue, the Working Formulation remains the most commonly used classification system for the diagnosis of lymphomas in the United States. Therefore, the classifications discussed in this review refer to this system. Under the Working Formulation, NHL is divided into low-, intermediate-, and high-grade lymphomas on the basis of histology (Table 1).<sup>8</sup> These categories serve as accurate prognostic indicators that describe the natural history of the disease, patterns of response to therapy, and disease-free survival in untreated patients.

At present, the staging system for NHL is the same as that for Hodgkin's disease (the Ann Arbor staging system, Table 2).<sup>10</sup> This system allows patients with Hodgkin's disease to be identified as those who are amenable to treatment with radiation therapy and those who require systemic chemotherapy for the treatment of more advanced disease. However, because most cases of NHL appear to be "systemic" or "multicentric" from the time of diagnosis, the system is of relatively less use in determining therapeutic options in NHL. For intermediate- and high-grade

NHL, a predictive model (the International Index) based on age, tumor stage, serum lactate dehydrogenase concentration, performance status, and number of extranodal sites was found to be more accurate than the Ann Arbor classification in predicting long-term prognoses of these patients.<sup>11</sup>

## Incidence of NHL in the Elderly

Data from the Surveillance, Epidemiology, and End Results (SEER) registry of the National Cancer Institute have shown that the average age-adjusted incidence of NHL is higher among individuals  $\geq 65$  years of age than in younger age groups.<sup>1</sup> The incidence of NHL increases with age in both men and women, as well as in racial subgroups (Fig 1).<sup>12</sup>

Although the reasons for this increase are unclear, several explanations are possible. For instance, increasing age is associated with a greater preponderance of immunologic deficits,<sup>13</sup> with abnormalities in T-cell proliferation,<sup>14</sup> and with changes in B-cell/T-cell interactions as well as in immunoglobulin gene selection in animal studies.<sup>15</sup> In addition, the risk of NHL is affected by long-term exposure to chemicals such as pesticides in the environment.<sup>16,17</sup>

### Incidence by Lymphoma Grade and Site

Incidence rates for each subgroup of NHL in the Working Formulation are available from the SEER registry. The incidence of each NHL grade was recently examined in a review of SEER data from 1973 to 1987.<sup>18</sup> These data are summarized below.

**Low-Grade Lymphomas** — Small lymphocytic lymphomas account for nearly 10% of all NHLs. The SEER data show that the incidence of small lymphocytic lymphomas correlates directly with increasing age; the age-specific incidence increases notably after 40 years of age and peaks at 10.0 per 100,000 individuals 80 to 84 years of age between 1983-1987 (Fig 2).<sup>18</sup> A direct correlation with age is also evident with follicular small cleaved cell lymphoma, most cases of which occur in individuals  $>30$  years of age. The age-specific incidence peaks at 6.4 per 100,000 individuals between the ages of 75 and 79 years.

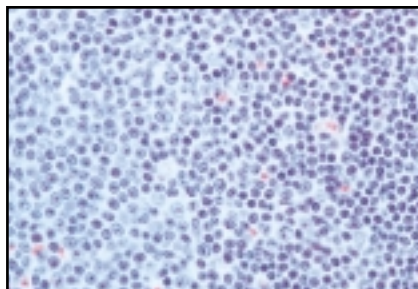


Fig 2. — Low-grade non-Hodgkin's lymphoma, small lymphocytic subtype. Photomicrograph courtesy of L. C. Moscinski.

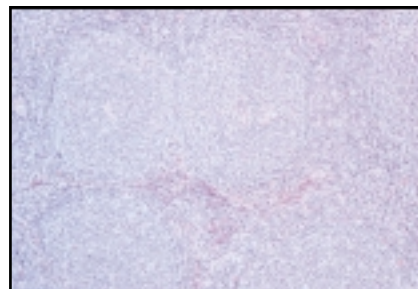


Fig 3. — Low-grade non-Hodgkin's lymphoma, follicular mixed cell subtype. Photomicrograph courtesy of L. C. Moscinski.

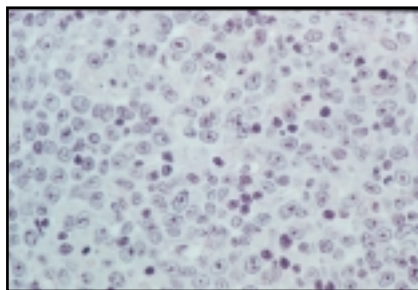


Fig 4. — Intermediate-grade non-Hodgkin's lymphoma, diffuse large cell subtype. Photomicrograph courtesy of L. C. Moscinski.

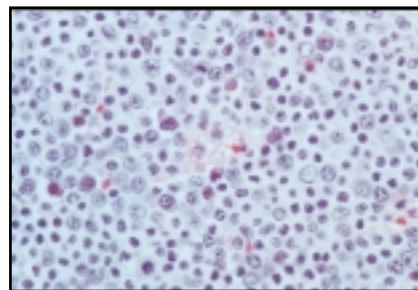


Fig 5. — High-grade non-Hodgkin's lymphoma, immunoblastic (T-cell) subtype. Photomicrograph courtesy of L. C. Moscinski.

Follicular mixed small cleaved and large-cell lymphomas comprise 5% of NHLs (Fig 3). Most cases are diagnosed in individuals  $>35$  years of age, and the age-specific incidence rate peaks at 3.3 per 100,000 individuals between the ages of 65 and 69 years.<sup>18</sup>

**Intermediate-Grade Lymphomas** — Follicular large-cell lymphoma is the least common intermediate-grade tumor, accounting for 2.6% of all NHLs.<sup>18</sup> The age-specific incidence increases gradually after 40 years of age, peaking at 2.1 per 100,000 individuals aged 75 to 79 years.<sup>18</sup>

The incidence of diffuse small cleaved cell lymphoma also increases with age, from 0.2 per 100,000 individuals 35 to 39 years of age to a peak of 7.9 among those 80 to 84 years of age.<sup>18</sup> Diffuse mixed small- and large-cell lymphoma accounts for 7.6% of all NHLs. The age-specific incidence is 0.3 per 100,000 persons aged 35 to 39 years and peaks at 8.0 among those aged 80 to 84 years.<sup>18</sup> Diffuse large-cell lymphoma is the most frequently occurring NHL and comprises more than 50% of all NHLs among individuals  $\geq 65$  years of age (Fig 4). The age-specific incidence rate rises from 0.3 per 100,000 persons 35 to 39 years of age to a peak of 26.6 among those aged 80 to 84 years.<sup>18</sup>

**High-Grade Lymphomas** — From 1983 to 1987, large-cell immunoblastic lymphomas constituted 5.5%

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of NHLs (Fig 5).<sup>18</sup> Again, the incidence of NHL increases gradually with age, peaking at 3.9 per 100,000 persons who were 85 years of age or older. However, the incidence of NHL also has been rising among individuals in the mid-30s to mid-40s age group, primarily because of the growing problem of AIDS among white men.<sup>18</sup>

the prognosis is similar to that associated with nodal tumors (with the exception of primary lymphoma of the central nervous system).<sup>23</sup> Specific types of extranodal tumors that occur mainly in individuals >60 years of age include primary lymphomas of the testes, epidural space, and skin (B-cell).<sup>20,25-30</sup>

Lymphoblastic lymphoma is the least common of the Working Formulation subtypes (with the exception of the miscellaneous group). The incidence does not correlate with increasing age.<sup>18</sup> Small non-cleaved cell lymphomas have been increasing in frequency (representing 3.4% of all NHLs in 1983 to 1987), partly due to the AIDS epidemic. The age-specific incidence shows a bimodal distribution, with a rate of 0.4 per 100,000 persons 5 to 14 years of age and 1.4 among those 75 to 79 years of age.

Although the data from the SEER program do not distinguish subtypes, these numbers probably reflect primarily Burkitt's lymphoma in the younger group and non-Burkitt's lymphoma in the older group. In addition, the incidence has been rising in the 30- to 39-year-old age group as AIDS has continued to spread.<sup>18</sup>

### *Prevalence by Lymphoma Grade*

Among patients with NHL, the prevalence of the various histologic subtypes is similar in older and younger individuals.<sup>19</sup> This pattern was evident in an analysis of data from our institution.<sup>20</sup>

These data showed that the prevalence of low-grade lymphomas was 31% in patients 64 years of age or younger vs 37% in their older counterparts. Intermediate-grade lymphomas comprised 44% of all NHL in the younger group vs 45% in the older group. The prevalence of high-grade lymphomas was 25% vs 18%, respectively. The stage of NHL also did not differ notably by age.

*Extranodal Lymphomas* — Approximately one half of all NHLs have extranodal involvement.<sup>19,24</sup> The most frequent site is the stomach, followed by the skin, brain, or nervous system; small intestine, colon, and rectum; and oral cavity.<sup>2</sup> Extranodal sites of involvement are more common in older than in younger patients, but

## Pathophysiology of NHL

Recent investigations into the pathophysiologic mechanisms underlying NHL have focused on three areas of inquiry.<sup>20</sup>

First, immunophenotypic studies have given rise to hypothetical schemata depicting normal B- and T-lymphoid differentiation. The stages are defined on the basis of reactivity with panels of monoclonal antibodies directed against maturation- or activation-associated antigens. The assumption is that neoplasms reflect clonal proliferations of neoplastic cells that are blocked at specific stages of cell differentiation. Many neoplastic phenotypes cannot be accounted for by this simplified approach. Also, the distinction between B-cell and T-cell neoplasia is currently of limited value in clinical management, except in the case of cutaneous T-cell lymphoma.<sup>9,31</sup> Nonetheless, these schemata are helpful in understanding lymphoma immunophenotypes. The maturational steps and corresponding histologic types of B- and T-cell-derived NHL are shown in Figs 6 and 7, respectively.

Second, additional insights into the pathophysiology of NHL have emerged from research on cell proliferation and DNA content. The proportion of cells in the S phase of the cell cycle (ie, proliferative fraction) has been shown to differ significantly among low-, intermediate-, and high-grade NHLs.<sup>32</sup> The S-phase fraction is typically <5% in low-grade, <10% in intermediate-grade, and >10% in high-grade NHLs. Notably, the S-phase fraction is also an independent prognostic indicator.<sup>33</sup>

A good correlation is also evident between DNA ploidy and histologic grade.<sup>32</sup> Generally, low-grade NHLs are more likely to contain DNA that is diploid or close to the diploid value (ie, having normal DNA content), whereas higher-grade NHLs are more likely to be aneuploid (ie, having more or less than normal DNA content but usually in the hyperdiploid range).<sup>32,34</sup>

Third, research on genetic markers has suggested that proto-oncogenes play a significant role in the pathophysiology of NHL. Proto-oncogenes are normal genes that help control cell proliferation and differentiation. Alteration of their structure or function can lead to induction or progression of lymphomas. In malignant cells, oncogenes perpetuate the proliferative response as the result of being activated at a point when their normal cellular counterparts would be inactive. Abnormal activation can result from chromosomal translocation, point mutation, or gene amplification. In NHL, however, point mutation or gene amplification is rare, and the main cause of abnormal oncogene expression is chromosomal translocation (such as *c-myc* in Burkitt's lymphoma, *bcl2* in follicular lymphomas, and *bcl1* in

Table 3. — Diagnostic Procedures for Non-Hodgkin's Lymphoma<sup>20</sup>

Perform initial diagnostic tests
- cytologic examination of needle aspirate if carcinoma suspected
- excisional biopsy
Consult a pathologist before biopsy, as inappropriate handling of the specimen may prevent the performance of some special tests (eg, flow cytometry and gene rearrangement analysis)
- in light of the potential need for the above-cited tests, a portion of the specimen should be deep-frozen
- when mycobacterial and fungal cultures are indicated, a portion of the specimen should be placed in sterile saline
Whenever possible, a hematopathologist should confirm the diagnosis; alteration of the original diagnosis is not uncommon and holds critical implications for treatment plans

intermediate-grade lymphomas). Based on a review of cytogenetic studies from 1,405 patients,<sup>35</sup> commonly reported recurring translocations in NHL include t(8;14)(24q;32q) and t(14;18)(32q;21q), and those recurring in <10% of cases include t(11;14)(13q;32q), t(3;22)(27q;11q), t(2;5)(23p;35q), and t(1;6)(21q;23q). Structural and numeric abnormalities include deletions of 1p22, 1q21-3, 6q21-5, and trisomies of chromosomes 7 and 12.<sup>35</sup> The translocations seen more frequently involve the gene encoding for the immunoglobulin heavy chain located in chromosome 14 and the *bcl2* gene located in chromosome 18: t(14;18) or the *myc* oncogene on chromosome 8: t(8;14). In patients with follicular lymphomas, t(14;18) is seen in 46% to 89% of cases and is associated with an indolent course. Also, t(14;18) can be seen in cases of intermediate- and high-grade histology and is often associated with abnormalities of chromosome 11.<sup>36</sup> In patients with Burkitt's lymphoma, t(8;14) is reported in 44% to 100% of cases but occasionally is seen in patients with intermediate-grade histology.<sup>35</sup>

## Clinical Presentation and Diagnosis of NHL

The clinical presentation of NHL is similar in older and younger individuals. Most frequently, NHL presents as painless lymph node enlargement. Malignancy is usually the underlying cause in the elderly, although nonmalignant factors should be considered as well.<sup>20</sup>

A needle biopsy and cytologic assessment of the aspirate should be performed if carcinoma is suspected,<sup>37</sup> and an excisional biopsy should be performed when the diagnosis of lymphoma is considered. Apart from standard histology, flow cytometry or immunohistochemistry usually are undertaken to confirm monoclonal proliferation.<sup>34,38</sup> In patients with undifferentiated tumors, B-cell lymphomas may be diagnosed via

lymphoid surface markers<sup>34,38</sup> or immunoglobulin gene rearrangement, and T-cell lymphomas may be diagnosed via detection of specific T-cell receptors.<sup>39</sup> Additional diagnostic guidelines are presented in Table 3.

The degree of effort directed toward establishing the clinical stage of disease varies according to the therapeutic goal. A complete blood cell count, chest radiographs, and serum lactate dehydrogenase levels should be obtained for every patient. If aggressive chemotherapy will be instituted to achieve a cure, then the patient should undergo bone marrow aspiration and biopsies with flow cytometry to determine the precise phenotype of the malignant clone, as well as computed tomography of the chest and abdomen.<sup>20</sup> A baseline gallium scan may be useful for comparison when evaluating areas of residual disease or relapse.<sup>40</sup>

## Treatment Strategies

### *Conventional Chemotherapy*

*Low-Grade Lymphomas* — Although low-grade NHLs are considered indolent, they are incurable with standard therapies, with the exception of the rare patient who presents with early-stage disease.<sup>41</sup> Both the response to conventional chemotherapy and the survival rate following relapse are generally less favorable in patients >60 years of age than in younger individuals.<sup>41,42</sup>

Regimens combining alkylating agents (chlorambucil or cyclophosphamide) and glucocorticoids are effective and well tolerated in the older population. However, patients with concomitant conditions (eg, hypertension, heart failure, diabetes, or osteoporosis) may not tolerate corticosteroids, and such drugs must be used with caution in these groups.<sup>20</sup> In a prospective, randomized study of 259 patients with low-grade NHL,<sup>43</sup> 127 patients received a doxorubicin-containing multidrug regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]), and 132 received chlorambucil/prednisone. While a higher remission rate was observed for the CHOP-treated patients, there were no statistical significant differences in survival. This was also true when comparing patients above and below the age of 65 years. Results reported in a retrospective analysis<sup>44</sup> of 415 patients included in various Southwest Oncology Group trials showed no statistical improvements in survival when compared with less aggressive regimens.

Treatment should be discontinued during periods of remission, then reinitiated during relapse. Typically, durations of remission become progressively shorter

and patients eventually become refractory to treatment. At that point, another lymph node biopsy should be performed to determine whether the disease has become more aggressive and thereby warrants a change in treatment approach.

*Intermediate-Grade Lymphomas* — Approximately 30% to 45% of all NHLs are intermediate-grade diffuse large-cell lymphomas.<sup>2,8,21</sup> The majority of intermediate-grade NHLs are large-cell lymphomas — the most common NHLs in elderly individuals.<sup>8,24</sup> Clinical trials have shown that chemotherapy can produce a complete response in approximately 37% or more of patients ≥60 years of age who have large-cell or other types of aggressive lymphomas.<sup>45-48</sup> Patients >60 years of age had complete remission rates comparable to those of younger patients, but their relapse rate was significantly higher. The difference was most striking among patients identified by the International Index as low-risk groups, resulting in a significant age difference in the survival of these patients. No significant age-related differences in survival were observed in high-risk groups.<sup>49</sup>

Regardless of the regimen chosen, doxorubicin or mitoxantrone should be incorporated if optimal responses are to be attained.<sup>20</sup> CHOP is among the most commonly used and well-tolerated regimens. In a recent randomized trial,<sup>50</sup> this regimen was associated with a complete response rate of 44% and a three-year disease-free survival rate of 41%. Compared with the CHOP regimen, no significant improvement in either response rates or survival rates was evident with newer regimens, including methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B); low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD); or prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM). Furthermore, fatal toxicity occurred in only 1% of the CHOP group compared with 3% of the ProMACE-CytaBOM group, 5% of the m-BACOD group, and 6% of the MACOP-B group. A higher rate of fatal toxicities was seen for patients >60 years of age in the MACOP-B arm, which accounted for a significantly poorer survival of older patients. Survival of older patients was similar to younger ones among those treated with CHOP, m-BACOD, or ProMACE-CytaBOM.<sup>51</sup> The use of CHOP entails administration of therapy every three weeks for a variable length of time. At least six treatment cycles should be administered, with an additional two cycles after complete response has been achieved.<sup>20</sup>

Since anthracyclines are cardiotoxic in a dose-dependent manner, this issue is particularly relevant to the older patient who may have a diminished cardiac reserve.<sup>52</sup> In a randomized trial<sup>53</sup> of patients >60 years of age with intermediate- and high-grade NHL, mitoxantrone was compared with doxorubicin as a potentially less toxic drug. However, significantly better complete remission and survival rates were demonstrated with CHOP-doxorubicin as compared with CHOP-mitoxantrone, with no significant differences in common toxicities. Two other randomized trials<sup>54,55</sup> have reported no significant differences in response rates, survival, or cardiac toxicities in patients receiving CHOP-doxorubicin compared with CHOP-mitoxantrone.

Liposomal formulations of anthracyclines and cardioprotective agents (dexrazoxane) may prevent cardiotoxicity and extend the tolerated doses of these active drugs.<sup>56</sup>

Alternatively, nonanthracycline-containing regimens have been developed for the elderly patient that can produce significant remission and survival rates.<sup>57</sup> Similarly, different treatment strategies are needed for the older patient with heart disease. A regimen combining cyclophosphamide, etoposide, prednisone, and procarbazine (CEPP) is preferable in this subset of patients,<sup>58</sup> even though the efficacy may be less than that associated with CHOP.

*High-Grade Lymphomas* — In the older population, most high-grade lymphomas are immunoblastic and can be managed with the same therapies used for large-cell NHLs.<sup>19</sup> In a recent retrospective study,<sup>59</sup> patients >60 years of age with high-grade NHL had a significantly poorer survival when compared with younger patients. However, age was not an independent prognostic indicator; the main survival advantage was conferred by completion of intensive treatment. Elderly patients given intensive therapy had a median survival of 50 months compared with 10 months for those treated less aggressively.<sup>59</sup> Patients with high-grade NHL in first complete remission may benefit from high-dose consolidation therapy with autologous bone marrow transplantation.<sup>60</sup>

### *Combined Use of Chemotherapy and Other Treatments*

*Low-Grade Lymphomas* — Combined treatment strategies are being evaluated as methods of improving outcomes in patients with low-grade NHLs. Among the approaches under consideration is the use of chemotherapy plus interferon- $\alpha$  (IFN- $\alpha$ ). In one randomized trial,<sup>61</sup> which also enrolled some patients with intermediate-grade NHLs, comparable responses were

obtained whether CHOP was used alone or in combination with IFN- $\alpha$ ; complete response rates were 29% and 32% and partial response rates were 57% and 54%, respectively. However, the duration of complete response was significantly longer in the group receiving IFN- $\alpha$ .

Another strategy under investigation entails the use of high-dose, intensive chemotherapy plus autologous bone marrow transplantation.<sup>62</sup> This approach can result in significant disease-free survival rates for high-risk patients who would have no curative potential with standard-dose chemotherapy.<sup>63</sup> While at increased risk for treatment-related morbidity and mortality, patients >60 years of age can be candidates for these treatment modalities.<sup>64</sup>

*Intermediate-Grade Lymphomas* — Some newer therapies may prove to be particularly useful in older individuals with intermediate-grade lymphomas. For instance, hematopoietic growth factors might be used to lessen the myelosuppressive effects of chemotherapy,<sup>65</sup> and free radical scavengers might be used to prevent doxorubicin- or mitoxantrone-induced cardiotoxicity.<sup>66</sup>

*High-Grade Lymphomas* — A randomized trial<sup>67</sup> of patients with high-grade NHLs has suggested that the administration of granulocyte-colony stimulating factor may help shorten the duration of neutropenia and lower the risk of infection in patients receiving chemotherapy.

### *Role of Purine Analogs*

An important advance in the treatment of NHL has been the development of new purine analogs, such as 2-chlorodeoxyadenosine (2-CDA, or cladribine), fludarabine monophosphate, and 2'-deoxycoformycin (DCF, or pentostatin). Clinical trials of these agents have enrolled patients of various ages, including those >60 years of age.

*Cladribine* — Kay et al<sup>68</sup> evaluated the use of cladribine in 40 patients aged 37 to 80 years with relapsed low-grade lymphomas who had failed conventional therapy. The overall response rate was 43%, with complete remission in 20% of patients and partial response in 23%. Of 17 patients who responded, 12 had been refractory to previous treatments. Similarly, Hoffman et al<sup>69</sup> reported a 43% response rate in 21 patients aged 18 to 72 years with advanced indolent NHLs (low- or intermediate-grade) who had failed to respond to standard chemotherapy or had progressed after an initial response. Of three patients (13%) who achieved a complete response, one was 60 years of age and one

was 72 years of age. In a study<sup>70</sup> of eight pretreated patients with low-grade lymphoma (none of whom was elderly), three patients responded to cladribine.

The major toxicities of cladribine are bone marrow suppression and immunosuppression.<sup>68,69</sup> However, clinical investigators have judged the overall toxicity profile to be acceptable.<sup>68</sup> Cladribine may be preferable to other purine analogs in the older patient due to the lack of neurotoxicity and its nondependence on renal clearance.<sup>71</sup> Some observers have suggested that cladribine may be used in escalating doses as intensive therapy, whereas fludarabine is subject to dose-limiting toxicities.<sup>68</sup>

**Fludarabine** — In an analysis of 57 patients aged 33 to 76 years with low- or intermediate-grade NHL who failed or relapsed after previous chemotherapy and radiation, the Eastern Cooperative Oncology Group found that fludarabine produced an overall response rate of 28%.<sup>72</sup> The responses included 18% complete remissions and 27% partial remissions in low-grade NHL, and 11% complete remissions and 6% partial remissions in intermediate-grade NHL. In subsequent work, this group reported a 15% complete response rate and 15% partial response rate among 62 patients aged 18 to 76 years with refractory or relapsed low-grade NHL.<sup>73</sup> In a study of 76 previously treated patients aged 19 to 77 years, Redman et al<sup>74</sup> noted a 55% response rate among 38 individuals with low-grade lymphomas but no responses in those with intermediate- and high-grade lymphomas (except for follicular large-cell lymphomas). Zinzani et al<sup>75</sup> obtained a 66% response rate in 21 patients aged 40 to 72 years with resistant or relapsed NHL. Three complete responses and three partial responses were achieved in eight previously untreated patients in this study. A recent study<sup>76</sup> reported the use of fludarabine as single agent in 54 untreated patients with advanced follicular NHL. In this cohort with a median age of 51 years (range 30 to 72 years), an overall response rate of 65% was observed, with a complete response rate of 37%.

Myelosuppression is the major toxicity of fludarabine.<sup>72,74</sup> Also of concern are a marked reduction in cell-mediated immunity, an increased risk of infection,<sup>74,77,78</sup> and central nervous system depression.<sup>73</sup> These toxicities appear to be dose-limiting.

**Pentostatin** — The Eastern Cooperative Oncology Group evaluated the use of pentostatin in 37 relapsed patients aged 19 to 80 years including 25 with NHL, three with Hodgkin's disease, eight with cutaneous T-cell lymphoma, and one with an unknown subtype.<sup>79</sup> Among 31 patients eligible for analysis, 10 (32%) had a partial response. In general, response rates have been

somewhat lower with pentostatin than with cladribine or fludarabine in patients with NHL.<sup>69,79-81</sup>

Because of the promising findings with purine analogs as single-agent therapy, studies are currently underway to examine purine analogs in combination with other drugs in untreated patients with NHL. The promising responses to purine analogs among the older individuals in these studies suggest that further investigations are warranted. Future work should yield additional information on the potential efficacy of these agents in this population.

## Conclusions

In light of the aging of the United States population, the increasing prevalence of NHL in the elderly is of growing concern. Hopefully, continued research not only will lead to more clinically useful classification systems, but also will augment our understanding of the pathophysiology of this disease. The introduction of newer therapies such as the purine analogs and the use of combination treatment strategies promise to improve clinical response rates. Clinicians who treat this population must remain abreast of these developments to ensure more effective management of NHL in the future.

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