

Part 3
Chapter

19

Management of hematologic malignancies in older adults

Management of non-Hodgkin's lymphoma in older adults

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A. Incidence

Non-Hodgkin's lymphoma (NHL) is currently the fifth most common malignancy in women and the sixth most common in men in the United States.¹ It is estimated that approximately 35,450 men and 30,670 women will be diagnosed with NHL in 2008, and 19,160 patients will die from this disease in 2008.² Over the last 2 decades, the incidence of NHL has been increasing across all adult age groups, rising by as much as 8–10 percent per year.^{3–6} Specifically, the incidence is rising in patients aged over 60 years.^{7–9} Among U.S. men, the incidence of NHL ranged from 13.1 per 100,000 in people aged 40–44 years to 51.2 per 100,000 in people aged 60–64 years and 133 per 100,000 in people aged 80–84 years.¹⁰ This increasing incidence is relevant in the elderly population; though patients aged over 65 years represent 13 percent of the population, 53 percent of all new cases occur in this age group. The median age of patients at diagnosis of NHL is 67 years. With the population over 75 years and 85 years tripling and doubling, respectively, by 2030, the occurrence of NHL in this older patient population will pose an increasing problem.^{6,11}

B. Impact of aging

Though overall progress in the management of cancer, and specifically NHL, has been made in the last few decades, cancer-specific mortality continues to increase as a function of age. In general, older patients have a number of factors, including concomitant medical conditions (comorbidities) and physiologic and functional changes, that can affect prognosis, treatment, and outcomes (Table 19.1).^{12,13} Kidney and liver function also decline as a natural part of aging. Ultimately, these factors may lead to modifications in treatment as well as changes in treatment outcomes.¹⁴ For example, though anthracyclines are known to improve survival in NHL patients, physicians may be reluctant to give chemotherapy to the elderly, and only 42 percent of 4,000 patients aged over 65 years

with diffuse large B-cell lymphoma received doxorubicin in a recent report.¹⁵ In terms of cognitive function, it is essential to consent patients for chemotherapy, yet up to 30 percent of the elderly have cognitive impairment.¹⁴ Depression remains a problem in the elderly, which can impair outlook on cancer care and treatment. Nutritionally, 40 percent of hospitalized cancer patients are at risk for or already have developed malnutrition. The social environment and access to care may also be a barrier. These issues can be challenges in the care of elderly patients with NHL.

Finally, the presence of comorbidities and polypharmacy may also influence a patient's care.¹⁴ In one study, 35 percent of patients between the ages of 65 and 79 years in the United States had at least two chronic diseases. This number, however, increased to 70 percent in patients over 80 years of age.¹⁶ The presence of comorbidities can lead to polypharmacy and potential drug interactions with chemotherapy. The presence of comorbidities may also lead to alterations in cancer outcome. Common comorbidities such as diabetes have been shown in one study to be associated with a worse cancer outcome.¹⁷ All these issues related to functional status, cognitive abilities, emotional conditions, comorbidities, nutritional status, polypharmacy, and the patient's social and environmental situation need to be considered in the care of these patients, leading to a multidisciplinary approach in treating the elderly with NHL.

Age is also a barrier to enrollment in clinical trials.¹⁸ Despite a high incidence of cancer in the elderly, older patients make up only 20 percent of those in phase II clinical trials. Although clinical trials remain the main approach for evaluating the safety and efficacy of cancer treatment, few elderly are actually enrolled in these trials.

While a number of factors influence the care of elderly patients with NHL, the question arises as to why older patients have a poorer outcome and whether the disease is biologically different in elderly patients. In clinical trials, however,

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Table 19.1 Factors influencing cancer care in the elderly.

Functional status
Cognitive abilities
Emotional conditions
Comorbid conditions
Nutritional status
Polypharmacy
Alterations in pharmacokinetics
Social and environmental situation

it has been demonstrated that if older patients with diffuse aggressive NHL receive full-dose chemotherapy, their outcome is comparable to that of younger patients.^{19–22} There is no difference in disease stage by age in patients with follicular, Burkitt's, or lymphoblastic lymphoma. Though not completely understood, elderly patients with diffuse aggressive NHL appear to have more advanced-stage disease.

C. Epidemiology and classification of non-Hodgkin's lymphoma (NHL) in the elderly

Risk factors for the development of NHL have been identified and are not specific for age. These risk factors include occupational exposures to agricultural herbicides, pesticides, or industrial solvents; alterations in the immune system, including autoimmune disorders and congenital and acquired immunodeficiencies; and the adminis-

tration of chronic immunosuppressive therapy as well as infectious etiologies. The latter include infections with HIV, human T-lymphotropic virus types I/II, Epstein Barr virus, *Helicobacter pylori*, *Borellia burgdorferi*, and *Chlamydia psittaci*.^{23,24}

Over the years, there have been a number of different classification systems used to differentiate the subtypes of NHL. In 2001, the World Health Organization incorporated a classification scheme that included morphologic, immunophenotypic, and genetic features as well as clinical aspects. Within the previously recognized Revised European American Lymphoma (REAL) classification schema that was developed in 1994,²⁵ all lymphoma subtypes may be observed in elderly patients.^{26,27} However, there tends to be a higher percentage of patients with aggressive lymphoma,²⁶ with elderly patients having a slightly higher tendency for developing lymphocytic/lymphoplasmocytic lymphoma, diffuse large B-cell lymphoma, and peripheral T-cell lymphoma (Table 19.2). Anaplastic large-cell lymphoma, lymphoblastic lymphoma, and Burkitt's lymphoma are less commonly seen in the elderly. It is unclear whether specific chromosomal or genetic abnormalities are associated with the development of NHL in the elderly, with few studies in this area. Additionally, extranodal sites of involvement are more common in older than in younger patients. Specifically, extranodal sites that commonly occur in patients over 60 years of age include primary lymphomas of the testes, epidural space, and skin (B cells).^{28–30}

Table 19.2 Frequency of different lymphoma reports in the REAL classification of patients according to age ($n = 1,283$).

Lymphoma subtype	No. pts	Patients in each age category (%)				
		≤30–35	35–49	50–59	60–69	≥70
Small lymphocytic	98	1	14	18	33	34
Mucosa-associated lymphoid tissue	108	9	14	24	26	27
Marginal zone (splenic and nodal)	32	6	22	22	34	16
Follicular	317	8	22	22	26	22
Mantle cell	72	–	11	31	33	25
Diffuse large B cell	448	16	15	16	21	32
Peripheral T cell	93	11	18	17	26	28
Anaplastic large T/null cell	32	53	19	6	13	9
Burkitt's	9	78	–	11	11	–
Lymphoblastic	28	68	14	14	4	–
Unclassified	46	6	22	20	22	30
All patients	1,283	13	17	19	24	27

Note. REAL = Revised European-American Lymphoma. Adapted from Coiffier et al.²³

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D. Staging and prognostic factors

The Ann Arbor staging system has been traditionally used to stage NHL.³¹ This staging system divides NHL into limited (stages I, II) and advanced (stages III, IV) disease. A staging evaluation should typically include a physical examination; a computerized tomography scan of the chest, abdomen, and pelvis and other sites as indicated; a bilateral bone marrow biopsy and aspiration; and laboratory tests. The bone marrow sample should be evaluated for standard histology, in addition to flow cytometry, immunohistochemistry, and cytogenetic analysis. Laboratory testing should include blood counts, lactate dehydrogenase (LDH), B2-microglobulin, and serologies for HIV and hepatitis B and C. The evaluation of baseline kidney and liver function should also be taken into consideration as alterations in these values may lead to a change in therapy.

E. Prognostic information

The International NHL Prognostic Factors Project (IPI) identified prognostic factors for patients with aggressive NHL treated with doxorubicin-based regimens (Table 19.3). Age, specifically over 60 years, was the most important factor independently associated with outcome. An advanced age resulted in a lower response rate and decreases in disease-free and overall survival (OS). This has subsequently been confirmed in other studies as well.^{19,20} The other poor prognostic factors identified by the IPI include an elevated LDH, poor performance status (PS 2–4), advanced-stage disease, and more than one site of extranodal involvement. Subsequent studies have identified the absence of cell surface expression of HLA-DR and beta-2 microglobulin with a poor response to treatment.^{32–34}

For patients with follicular lymphoma, a similar prognostic scheme, known as the FLIPI index,

Table 19.3 International Prognostic Index (IPI) and Follicular Lymphoma International Prognostic Index (FLIPI).

IPI	FLIPI
Age > 60 years	Age > 60 years
Stage III, IV	Stage III, IV
Lactate dehydrogenase > normal	Hemoglobin <12 g/dL
No. extranodal sites ≥ 2	No. extranodal sites > 4
Performance status ≥ 2	Lactate dehydrogenase > normal

was developed. The five prognostic indicators include age (less than or more than 60 years), Ann Arbor stage, hemoglobin (over or under 12 g/dL), number of involved nodal areas (more than or less than 4), and LDH. With these five indicators, three risk factor groups have been identified with low- (no or one adverse factors), intermediate- (two factors), and poor-risk (three or more adverse factors) disease associated with 10-year overall survival of 71 percent, 51 percent, and 36 percent, respectively.

F. Therapy of diffuse large B-cell lymphoma in the elderly

For decades, the standard approach to diffuse large B-cell lymphoma in the elderly consisted of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) chemotherapy.³⁵ In patients aged 65–75 years, CHOP chemotherapy resulted in complete remission rates of 50 percent. In patients under 75 years of age, complete remission rates were 40 percent with a median remission duration of 16 months. The basis for the CHOP regimen resulted from an intergroup trial in which CHOP was compared to other combination chemotherapy regimens (m-BACOD [methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine, dexamethasone], Pro-MACE-CytaBOM, MACOP-B), with no significant difference in efficacy (complete remission [CR], overall response [OR], progression-free survival [PFS]) being found but fewer adverse events seen with CHOP therapy.³⁶

Over the last decade, the introduction of the monoclonal antibody targeting CD20, rituximab, has led to a new standard of care (Table 19.3). Initially, rituximab therapy was studied in 40 patients with low-grade B-cell NHL.^{37–39} This study demonstrated a prolonged remission duration and a favorable safety profile. Subsequently, rituximab has been studied in combination with CHOP chemotherapy (R-CHOP). An initial phase II trial examined 33 patients with aggressive lymphoma who received six cycles of chemotherapy with R-CHOP.⁴⁰ Rituximab, 375 mg/m², was given 2 days before CHOP. Ten of these 33 patients were over 60 years of age. The overall response rate was 94 percent (61% CR, 33% partial remission [PR]) at a median follow-up of 26 months. Rituximab was generally well tolerated in all ages, including the older patients.

In a subsequent phase III trial of the Groupe d'Etude des Lymphomes de l'Adulte, Coiffier and

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colleagues reported the results of 399 patients aged 60–80 years with untreated diffuse large B-cell lymphoma who were randomized to either R-CHOP or CHOP chemotherapy.⁴¹ Rituximab, 375 mg/m², was given on day 1 of each cycle. The complete response rate, at an initial median follow-up of 2 years, was 76 percent for R-CHOP as compared with 63 percent for the CHOP arm ($p = .005$). In the most recent report with 7 years of follow-up, event-free, disease-free, and overall survival all continued to be significantly better in patients treated with R-CHOP than with CHOP.⁴² The 7-year overall survival advantage was present across all age groups. Specifically, for patients aged 60–69 years, overall survival was 58 percent with R-CHOP versus 40 percent with CHOP; for ages 70–74 years, 55 percent versus 41 percent; and for ages 75–80 years, 41 percent versus 21 percent, respectively. The 7-year overall survival was also favorable in those with poor risk characteristics (age over 75 years, PS = 2, presence of B symptoms, stage IV disease, elevated LDH, and the presence of marrow involvement).

In the subsequent phase III U.S. intergroup trial,⁴³ 632 patients with untreated diffuse aggressive NHL were randomized to therapy with R-CHOP or CHOP for a maximum of eight cycles. Two doses of rituximab, 375 mg/m², were given prior to cycle 1, with an additional dose of rituximab administered prior to cycles 3, 5, and 7. The 415 patients with an initial response to therapy (CR or PR) underwent a second randomization to either maintenance rituximab (375 mg/m² weekly for 4 weeks, given every 6 months for 2 years) or observation. Of these 415 patients, 352 were considered evaluable. The overall response rate to induction chemotherapy was 77 percent with R-CHOP and 76 percent with CHOP. With a median follow-up of 5.5 years, the 6-year failure-free survival was 45 percent in those who received maintenance rituximab and 36 percent for those randomized to observation.⁴⁴ For those patients receiving CHOP induction therapy, the median time to treatment failure (TTF) was 5.2 years with maintenance rituximab and 1.6 years with maintenance observation ($p = .0004$). In contrast, in those patients who received R-CHOP induction therapy, the median TTF was comparable among the two groups (5.6 years with maintenance rituximab group and 5.4 years with observation). In a weighted analysis, the use of maintenance rituximab did not change overall survival, regardless of the type of induction therapy received. Overall, these large phase III trials led to R-CHOP becoming

the standard of care in the treatment of aggressive lymphoma, including both elderly and young patients.

Finally, the German Lymphoma Study Group has subsequently studied the administration of CHOP chemotherapy on an every-14-day schedule (CHOP-14) as opposed to the more traditional every-21-day schedule (CHOP-21).⁴⁵ Initially, the group randomized patients to CHOP-14 versus CHOP-21 (CR 70% vs. 60%), CHOEP-14 (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone), or CHOEP-21 (71.6% vs. 76.1%). The addition of etoposide to CHOP, however, appeared to be more toxic in this patient population. In the subsequent RICOVER-60 study, 1,222 patients aged 61–80 years⁴⁶ were randomized to therapy with CHOP-14 or CHOP-R-14. This study included patients with stage I disease. Overall, the CR rates improved with the addition of rituximab (68% CHOP-14, 78% R-CHOP-14 after six cycles). With a median follow-up of 35 months, the 3-year event-free survival after six cycles of CHOP-R-14 chemotherapy was 67 percent compared to 47 percent with CHOP-14. Improvements were also seen in PFS (56.9% CHOP-14, 73.4% R-CHOP-14, $p = .0001$) and OS (67.7% CHOP-14, 78.1% R-CHOP-14, $p = .0181$) with the addition of rituximab. CHOP-R-14 was well tolerated in these older patients. However, Tholstrup and colleagues subsequently reported an analysis of 65 patients treated with CHOP-14, stratifying the patients into high-risk (age over 75 years with PS over 3) and standard-risk (age 60–75 years with PS less than 3 or age less than 60 years) subgroups.⁴⁷ There was a higher frequency of hospitalizations (88% vs. 68%) in the very high risk group, with most of these hospitalizations due to opportunistic infections, malnutrition, and declining performance status.

On the basis of these studies, it appears that R-CHOP therapy is well tolerated in the elderly (Table 19.4). The feasibility of delivering full-dose CHOP chemotherapy has been advocated.^{48–51} Campbell and colleagues found that the subset of patients ($n = 60$) at least 65 years of age with a favorable PS (less than 2) and few comorbidities could tolerate CHOP without growth factor support.⁴⁹ Jacobson and colleagues reported that full-dose CHOP with prophylactic growth factor support could be administered to patients over the age of 60 years with a low rate of neutropenia and neutropenic fever.⁵¹

Though it appears that R-CHOP is both effective and tolerated, a number of approaches have

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Table 19.4 The use of R-CHOP/CHOP in the elderly.

Trial (reference)	n	Age (years)	IPI (%)				DFS and OS	
GELA ^{41,42}	399	60–80 (median 69)						
8 cycles			0–1	2	3	4–5	(at 5 years)	
R-CHOP	202		14	32	39	15	66%	58%
CHOP	197		12	35	42	12	45%	45%
U.S. intergroup ^{43,44}		≥60						
Induction: 6–8 cycles	632							
			1	2	3	4–5		
R-CHOP	267	Median 69	12	35	44	9		
CHOP	279	Median 70	14	36	41	9		
Maintenance	415							
Rituximab	174							
Observation	178							
RICOVER-60 ⁴⁶	1,222	61–80						
			1	2	3	4–5	(at 3.5 years)	
R-CHOP-14 X 6		Median 69	31	29	25	15	73.4%	78.1%
R-CHOP-14 X 8		Median 68	30	27	25	18	68.8%	72.5%
CHOP-14 X 6		Median 68	32	26	26	16	56.9%	67.7%
CHOP-14 X 8		Median 68	30	29	26	16	56.9%	67.7%

Note. CHOP = cyclophosphamide, adriamycin, vincristine, and prednisone; R-CHOP = rituximab + CHOP; GELA, Groupe d'Etude des Lymphomes de l'Adulte; IPI = International Prognostic Index; DFS = disease-free survival; OS = overall survival.

been taken to minimize therapy-related toxicity while maximizing outcome in the elderly population. The use of non-anthracycline-containing regimens has been studied. The administration of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) was found to result in a lower CR rate and shorter survival compared with anthracycline-containing regimens.⁵² In a phase III trial of the Dutch Cooperative Hematology Group, 145 patients over 65 years of age were randomized to CHOP or cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP).⁵³ In this trial, the CR rate for CHOP was 49 percent and CNOP was 31 percent ($p = .03$) with a statistically significant prolongation in OS in the CHOP group ($p = .029$). In this trial, toxicities were similar, except for less nausea and alopecia with CNOP. In some other studies in which mitoxantrone was used, fewer cardiac complications occurred, but there was a significant amount of myelotoxicity.^{54–58} Other anthracyclines, such as idarubicin and epirubicin, have been utilized in CHOP or P-VABEC-like regimens with acceptable toxicities.^{59–61} Additionally, the administration of liposomal doxorubicin has been studied in the elderly. In phase II trials, pegylated liposomal dox-

orubicin was substituted for standard doxorubicin in the CHOP regimen (CCOP).^{62,63} Within one of these phase II trials, in which 33 patients over 60 years of age were treated, the overall response rate was 64 percent (49% CR, 15% PR). Sixty-four percent of patients developed grade 3 or 4 neutropenia.⁶³ It appears that liposomal doxorubicin may be an acceptable alternative; however, further randomized trials need to investigate whether this is well tolerated and truly less toxic. Finally, lower-intensity CHOP has been administered to patients over the age of 80 years and may prolong survival.²⁶ Italiano and colleagues reported the results of 24 patients over the age of 80 years treated with R-CHOP at a mean dose reduction of 30 percent. The overall response rate was 79 percent with a 2-year OS of 63 percent.⁶⁴

For elderly patients with cardiac disease, liposomal doxorubicin can be substituted for standard doxorubicin. The combination of pegylated liposomal doxorubicin to chemotherapy with vincristine, prednisone, and cyclophosphamide has led to overall response rates of 64–74 percent with CR of 49–59 percent.^{62,63} In these two phase II trials, ejection fraction appeared to be stable; however, the follow-up of these patients was limited.

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In patients who specifically have an absolute contraindication to doxorubicin chemotherapy such as an ejection fraction less than 30 percent, few data exist as to how to treat these patients. In one study of 83 patients with aggressive NHL, patients were treated with cyclophosphamide, etoposide, procarbazine, and prednisone (CEPP).⁶⁵ Of 75 evaluable patients, 40 percent achieved a CR and 32 percent had a PR. Twenty-one out of 61 (34%) patients with recurrent disease achieved a CR. On the basis of these results, though the data are limited, the use of CEPP for patients with a contraindication to doxorubicin would be favored. There may also be a role for treating these patients simultaneously with an angiotensin-converting enzyme inhibitor or beta-blocker concomitantly with chemotherapy, although additional studies are warranted to clarify the role of these medications for prophylaxis.^{66,67}

Approaches to improve the outcome of elderly patients with diffuse aggressive NHL have also focused on ameliorating myelotoxicity and subsequent infectious complications with myeloid growth factor support with conflicting results.^{68–70} In one study of 389 patients aged 65–90 years (median 72) years with aggressive lymphoma, in which patients were randomized to CHOP or CHOP plus filgrastim administered days 2–11, the CR rates (CHOP 55%, CHOP-filgrastim 52%, $p = .63$) and OS rates were comparable, with a median follow-up of 33 months. In this study, there was no difference in the numbers of grade 3–4 infections, hospital admissions, or days in the hospital.⁶⁸ Osby and colleagues reported differing results⁶⁹ in a study of 455 patients aged 60–86 (median 71) years who were randomized to CHOP or CNOP, alone or with filgrastim support (given on day 2 to day 10–14). Patients treated with CHOP had higher OS rates than those receiving CNOP ($p < .001$). The administration of filgrastim in conjunction with chemotherapy resulted in a reduction in grade 4 neutropenia and neutropenic fever. In addition, the relative dose intensity (RDI) was over 90 percent in those who received filgrastim support. Gomez and colleagues subsequently reported results of a phase II study in which 26 patients over 60 years of age (median 67 years) received CHOP plus sargramostim (given on days 4–13).⁷⁰ No difference in response rates or median survival was found among patients aged 61–69 years as compared to those aged over 70 years. However, patients 60–69 years of age received 86/90 planned cycles of chemotherapy, and those 70–84 years of age received only 52/72

planned cycles ($p = .00008$). The rates of neutropenia (absolute neutrophil count under 500), thrombocytopenia (platelets under 20,000), and febrile neutropenia were all significantly greater in patients over 70 years old as compared to those 61–69 years of age (neutropenia 24% vs. 73% of cycles of chemo, thrombocytopenia 5% vs. 42%, and febrile neutropenia 8% vs. 42%, respectively).

To better delineate who may benefit from the administration of hematopoietic growth factors, risk factors for the development of first-cycle neutropenia with CHOP chemotherapy in the elderly have been studied. In the study by Gomez and colleagues,⁷¹ while hypoalbuminemia (albumin less than 3.5), an elevated lactate dehydrogenase, and the presence of marrow involvement were predictive of first-cycle neutropenia, age and performance status were not. In the U.S. intergroup study, risk factors for the development of first-cycle neutropenia with the administration of CHOP or R-CHOP chemotherapy were advancing age, PS 2–3, hemoglobin less than 12 g/dL, an elevated lactate dehydrogenase, and a high or intermediate-high IPI score.⁷² Other studies have also identified kidney disease as a potential risk factor. Since these studies have been performed, the American Society of Clinical Oncology has developed guidelines for the use of growth factor support during the administration of chemotherapy.⁷³ For chemotherapy regimens in which the rates of neutropenia are predicted to be over 20 percent (CHOP-14, BEACOPP, etc.), prophylactic growth factor support should be administered with the first cycle of chemotherapy. For regimens in which the predicted rates of neutropenia are 10–20 percent (CHOP-21), prophylactic growth factor support should be considered with the first cycle of chemotherapy, particularly in the elderly. Any patient with a prior history of neutropenia should also receive prophylactic growth factor support with subsequent chemotherapy cycles.

Within the elderly population with aggressive lymphoma, full-dose R-CHOP appears to be the most efficacious treatment regimen. Guidelines for the use of hematopoietic growth factors exist and should be utilized as needed. It was shown in the U.S. intergroup trial that maintenance rituximab does not improve overall survival in patients who have received R-CHOP. Questions that remain unanswered include the optimal number of chemotherapy cycles and whether a 14-day or 21-day cycle interval is best. Studies are currently under way to further examine these questions.

G. Therapy of follicular lymphoma in the elderly

Approximately 30–40 percent of NHL in the elderly are follicular low-grade NHL. Unlike the diffuse aggressive lymphomas, the majority of clinical trials for the therapy of follicular lymphoma include both younger and older patients. As a result, there are limited data that focus specifically on the elderly. Patients usually present with an indolent onset of symptoms, typically with lymphadenopathy, hepatosplenomegaly, and advanced-stage disease. The presence of B symptoms is rare. Compared with other NHL, the follicular lymphomas are characterized by prolonged survival.^{74–76} Though a high percentage of patients will achieve an initial complete remission following treatment with single alkylating agents, combination chemotherapy, or combined-modality treatment, a continuous rate of relapse is observed.⁷⁴ Median survival in the elderly ranges from 5 to 7 years.⁷⁷

Patients with limited-stage (stage I–II) follicular NHL are generally treated with involved field radiation therapy, which typically results in long-term remissions.⁷⁸ In a report from Stanford University of 177 patients with stage I–II follicular lymphoma treated with involved field radiation, the median survival was 13.8 years with 5-, 10-, 15-, and 20-year survival rates of 82 percent, 64 percent, 44 percent, and 35 percent, respectively.⁷⁹ Similar results have been reported from other studies.^{80,81} In one series, there was no difference in the CR rate by age, and although OS was shorter in older patients, the lymphoma-specific death rate did not vary by age.⁸²

The initial approach of “watch and wait” in the elderly population has also been examined.⁷⁴ Advani and colleagues reported results of 43 patients with early-stage disease for whom therapy was deferred. Although the median age of the group was 58 years, 17 percent of the patients were over 60 years of age. With a median follow-up of 86 months, 63 percent of patients had not yet received therapy. Survival was comparable to historical series of patients receiving immediate treatment. The initial approach to watchful waiting has also been studied in patients with advanced disease, particularly in the elderly.^{83–85} In one study of 309 patients with stage III and IV follicular lymphoma, patients were randomized to observation or chlorambucil 10 mg continuously. At a median follow-up of 16 years, the OS was comparable between the treatment and observation groups (*p*

= .84). The actuarial chance of no treatment at 10 years from diagnosis was 19 percent (40% in those over the age of 70 years).⁸³ These results have been supported by additional trials as well.^{84,85}

In follicular lymphoma patients with advanced disease who require treatment, a variety of therapies have been utilized over the last decade, including conventional cytotoxic agents, single-agent rituximab, rituximab-containing regimens, and radiopharmaceuticals such as tositumumab or ibritumomab tiuxetan. Some studies indicate that the CR rate with single alkylating agent therapy approaches 50 percent.^{86,87} When combination chemotherapy is used, the CR rate is higher (60–80%).^{88–91} However, when single-agent alkylators such as cyclophosphamide and chlorambucil were compared with combination chemotherapy such as cyclophosphamide, vincristine, and prednisone (COP), significant differences in long-term outcome, including survival, were not observed. In a large trial by the Cancer and Leukemia Group, single-agent cyclophosphamide was found to result in a similar outcome to anthracycline-based combination chemotherapy in previously untreated follicular lymphoma patients.⁹² In this study, 228 patients were randomized to cyclophosphamide or CHOP with bleomycin. The median age of these patients was 56 years; slightly more than one-third of the patients were over 60 years of age. With 10-year follow-up, the overall times to failure and survival were similar in both groups. Toxicities were more common in patients receiving combination therapy. Other combination conventional cytotoxic therapies have also been studied in follicular lymphoma with similar results.⁹³

Rituximab has been studied both as a single agent and in combination with chemotherapy in the treatment of follicular lymphoma. Several phase II trials demonstrated the utility of single-agent rituximab as initial therapy and in the relapsed setting.^{94–98} In patients with relapsed or refractory disease, single-agent rituximab was found to have activity in patients over 60 years of age.^{94–96} In the study of Hainsworth and colleagues, rituximab was administered as first-line and maintenance therapy to follicular lymphoma patients with a median age of 65 years (range to 89 years), with an overall response rate of 73 percent, including 37 percent complete responses.⁹⁷ In another trial of 50 patients with stage II–IV follicular lymphoma, the overall response rate with single-agent rituximab at 50 days was 73 percent. By polymerase chain reaction (PCR) testing for the bcl-2 rearrangement in the

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peripheral blood and bone marrow, 57 percent and 31 percent of the patients became negative, respectively.⁹⁹ In these studies, rituximab appears well tolerated, particularly in the elderly population.

Rituximab has also been studied in combination with chemotherapy (cyclophosphamide, vincristine, prednisone [CVP] or CHOP).^{38,100,101} In a meta-analysis by Schultz and colleagues in which seven randomized controlled trials with a total of 1,943 follicular, mantle cell, or other indolent lymphomas were evaluated, therapy with rituximab in combination with chemotherapy (R-chemo) resulted in a higher OS and overall response (OR). Therapy with R-chemo resulted in prolonged OS (HR for mortality 0.65) as compared to chemotherapy alone. This overall survival benefit with R-chemo was seen in both follicular and mantle cell histologies (HR 0.63 and 0.60, respectively).¹⁰⁰ The German Low Grade Lymphoma Study Group also examined rituximab plus chemotherapy in 428 patients with untreated, advanced-stage follicular lymphoma who were randomized to CHOP or R-CHOP treatment.¹⁰¹ The median age of patients receiving R-CHOP was 54 years (range 29–82), with 37 percent of the patients being over 60 years of age. The median age of patients treated with CHOP was 57 years (range 27–79), with 41 percent of the patients being over 60 years of age. The addition of rituximab to CHOP chemotherapy resulted in an increased time to treatment failure ($p < .001$) and an improved overall response rate (96% vs. 90%, $p = .11$). The incidence of death during treatment was 1 percent in both arms, in which death was most commonly attributable to infection or lymphoma. R-CHOP therapy was beneficial in both younger and older patients.¹⁰¹

In follicular lymphoma, other agents, such as galiximab, CD80 monoclonal antibody, interferon, and radioimmunotherapy with tositumumab and ibritumomab, are also being further investigated in their role in the treatment of follicular lymphoma.^{102–105}

H. The role of transplantation in the elderly with NHL

The majority of patients with relapsed or refractory B-cell NHL are older than 60 years of age, yet they are often denied potentially curative high-dose therapy and autologous stem-cell transplantation (SCT) because of the risk of excessive treatment-related morbidity and mortality. A few

studies have demonstrated that it is possible to mobilize peripheral blood progenitor cells and to successfully undertake autologous SCT in patients over 60 years of age.^{106–108} Jantunen and colleagues reviewed the results of autologous SCT in 88 NHL patients over 60 years of age treated between 1994 and 2004 at six Finnish transplant centers.¹⁰⁹ The median patient age was 63 years, with 17 patients being over 65 years of age, with histologies including diffuse large B-cell ($n = 29$), mantle cell ($n = 27$), follicular ($n = 15$), peripheral T cell ($n = 12$), and other ($n = 5$) lymphoma subtypes. With a median follow-up of 21 months, 57 percent of patients were still alive, and 11 percent had early treatment-related mortality defined as death before day 100. The relapse rate after autologous SCT was 36 percent. Jantunen and colleagues also reviewed the experience of the European Blood and Marrow Transplant registry, in which 463 patients over 60 years of age (median 63, range 60–74) with diffuse large B-cell lymphoma underwent autologous SCT between 2000 and 2005.¹¹⁰ The outcome of these patients was compared with a younger cohort of diffuse large B-cell lymphoma patients who received autologous SCT during this same time period. When compared with younger patients, the older patients had more often received at least two prior therapies, were less commonly in first complete remission, and received their transplant at a later time after diagnosis. With 3-year follow-up, the nonrelapse mortality in the elderly cohort was 10.8 percent compared to 6.5 percent in the younger cohort ($p = .002$). Most of these deaths were attributable to infections, which occurred equally in the young and old cohorts; however, the rate of second malignancies was higher in the elderly population. The relapse rate was 38 percent versus 32 percent ($p = .006$), and OS was 60 percent versus 70 percent ($p < .001$), respectively. It appears from these studies that autologous SCT in patients over 60 years of age is feasible. Additional prospective studies need to address measures to reduce the treatment-related mortality. Myeloablative allogeneic sibling SCT has been studied to a lesser degree in patients over 60 years of age and also warrants further investigation.¹¹¹

I. Summary

The approach to management of elderly patients with NHL will continue to be a significant issue, with the median age of these patients being over

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60 years of age and in a setting in which the proportion of elderly patients in the population is increasing. The treatment of this patient population requires a multidisciplinary approach, given that most of these patients have comorbidities that can have an impact on the therapies being offered. Though clinical trials have expanded the knowledge base of practitioners caring for patients

with NHL, most of these trials have been limited to younger, healthy patients. Future prospective studies are needed not only to investigate the efficacy of therapy in older patients but also to evaluate the toxicity profiles of these treatments. Results of these studies will be crucial in defining optimal treatment approaches in these older patients.

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