Non-Hodgkin’s lymphoma in patients 80 years of age or older

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Background: Very elderly patients (≥80 years old) with non-Hodgkin’s lymphoma (NHL) frequently have co-morbid conditions and are generally excluded from clinical trials or even from treatment. The optimal treatment of these patients is unknown.

Patients and methods: We reviewed the records of 109 patients ≥80 years at diagnosis of NHL (65 F/44 M; median age: 84 years, range: 80–95).

Results: Seventy-eight patients (72%) had aggressive NHL, 25 (23%) had indolent NHL, eight had unclassified disease. Advanced-stage disease was noted in 54%. Forty patients (39%) had a poor ECOG performance status (PS), and 52 (49%) had an intermediate or high risk International Prognostic Index (IPI). Seventy-nine patients (72%) were treated with chemotherapy and 37 (34%) with radiotherapy. Initial chemotherapy consisted of chlorambucil in 15, oral etoposide in 2, and combination protocol in 62. Only 16% of patients received full-dose therapy, and only 50% completed ≥6 cycles of combination chemotherapy. The overall response rate for the 69 evaluable patients was 84% (complete 56.5%, partial 27.5%). Overall 5-year survival for the whole group was 39%, and median survival time was 26 months.

Conclusion: A high response rate can be achieved in very elderly NHL patients despite aggressive histology, poor prognostic features, and reduced doses of chemotherapy. Age alone should not be a contraindication to treatment.

Key words: combination chemotherapy, non-Hodgkin’s lymphoma, radiotherapy, survival, very elderly patients

Introduction

The number of people living longer than 65 years has more than doubled over the last century and it is expected to double again over the next 50 years, and to quadruple for the over-85-year age group [1].

Non-Hodgkin’s lymphoma (NHL) is the sixth most common cancer, and the sixth most common cause of death in men and the seventh in women [2]. The risk of NHL rises with age, from 0.15 (1 in 658) from birth through age 39 years to 1.25 (1 in 80) from age 60 to 79 years (1). Moreover, the incidence of NHL has been increasing by 1–2% annually over the past 2 decades, most dramatically in people over 60 years old. The greatest change in incidence was noted in older (75–84 years) white men, in whom the rate rose from 19 per 100 000 person-years to 99 per 100 000 person-years [3].

Accordingly, NHL has become an increasingly important cause of morbidity and mortality in the aging population. Age greater than 60 years is a recognized adverse prognostic factor for NHL. Overall survival decreases with increasing age, and patients over 70 years old have worse outcomes than patients 60 to 70 years old [4]. Several factors may account for this finding [5]:

- Differences in disease biology by age group.
- Presence of co-morbid illnesses which are more common in the elderly.
- Altered pharmacokinetics in the elderly and poorer host tissue tolerance.
- Changes in bone marrow hematopoietic reserve and microenvironment with increasing age, which may lead to increased treatment-related myelotoxicity.
- Higher rate of treatment-related complications, such as infections and cardiovascular events.
- Reluctance of primary physicians to refer older patients to hematologists and medical oncologists [6] and the reluctance of treating physicians to administer full doses of chemotherapy and aggressive protocols. An estimated 23% of older patients receive reduced and possibly inadequate doses of chemotherapy simply because of age [7].

As a result, the optimal management of very elderly patients (over age 80 years) is of considerable importance, but has not been defined. Van Spronsen et al. [8] studied the age-specific prevalence of co-morbidity in 904 patients with NHL. They found that 20% of patients younger than 60 years had at least...
one co-morbid condition, compared to 43% of patients 60–69 years old and 61% of patients aged over 70 years. Almost all trials which did include older patients excluded those with co-morbid illness [8]. Thus, there is a great need for randomized clinical studies of alternative or attenuated treatment options that focus specifically on the older patient population with concomitant diseases.

Recently, major progress was achieved by Coiffier et al. [9] in the treatment of patients with aggressive NHL aged 60–75 years with good performance status (0–2) and no serious active concomitant disease. In a randomized trial, these authors showed that combining CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with anti-CD20 antibody (rituximab) yielded a significantly better complete response rate and overall survival than CHOP alone (76% versus 63% and 70% versus 57% respectively). Pfreundschuh et al. [10] went even further and evaluated the effect of time-intensification of CHOP in patients aged 61–75 years. They found that shortening treatment intervals from 3 to 2 weeks (CHOP-14) significantly increased the time to treatment failure (relative risk 0.73; \( P = 0.024 \)) and overall survival (relative risk 0.62; \( P = 0.002 \)).

These studies suggest that patients up to 80 years old with NHL can tolerate and benefit from aggressive chemotherapy combined with immunotherapy. However, very little if any information is available for NHL patients older than 80. The aim of the present study was to review characteristics of NHL patients aged 80 years or more at diagnosis and to summarize our experience in their management and outcome.

patients and methods

We reviewed the hospital records of all patients diagnosed with NHL at three hematology centers in Israel between 1984 and 2004 who were age 80 years or older at diagnosis. All patients found were included. Clinical and laboratory data were retrieved from the hospital databases. The diagnosis of NHL was established by tissue biopsy and classified according to the WHO classification of tumors [11]. Bone-marrow biopsy was performed in 78 patients (72%). Serum \( \beta-2 \)-microglobulin (\( \beta-2 \)-M) level was measured by immunoassay (upper limit of normal, 1.81 mg/l). All patients were evaluated with the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) and the International Prognostic Index (IPI) [12]. Cumulative Illness Rating Scale (CIRS) applied score 0 if no organ system was compromised, or 1, 2, 3 score if an organ system (heart, blood pressure, vascular, respiratory, ENT, upper gastrointestinal, lower gastrointestinal, liver, renal, genitourinary, musculoskeletal, endocrine/metabolic, neurological) demonstrated mild, moderate or severe illness impairment respectively [13]. The intention to treat regimen was considered adequate if the same therapeutic protocol would have been chosen for a young lymphoma patient (even when reduced doses and fewer cycles were administered).

statistical analysis

Statistical analysis was performed using the SPSS 12.1 software program (SPSS Inc., Chicago, IL). For statistical analysis, patients were divided into subgroups as follows: I. extranodal disease: group 1 = 0, group 2 ≥1; II. PS score: group 1 = 0–1, group 2 = 2–3; III. IPI score: group 1 = 1–2, group 2 = 3–5; IV. chemotherapy protocol: group 1 = no treatment, group 2 = mild chemotherapy, namely, chlorambucil, COP (cyclophosphamide, vincristine, prednisone), FC (fludarabine, cyclophosphamide), group 3 = aggressive chemotherapy, namely, CHOP, R-CHOP, CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone), CEPP (cyclophosphamide, etoposide, procarbazine, prednisone), EMP (etoposide, mitoxantrone, prednisone), DHAP (dexamethasone, cisplatin, cytarabine), DVIP (dexamethasone, etoposide, ifosfamide, cisplatin); V. number of chemotherapy cycles: group 1 = 1–3, group 2 = 4–6, group 3 = ≥7; VI. percent of treatment dose administered: group 1 = 40%, group 2 = 50–75%, group 3 ≥80%; VII. response: group 1 = complete response, group 2 = partial response, group 3 = no response. Event-free survival (EFS) and overall survival were calculated from the date of diagnosis to the date of disease progression, relapse, or death using the product-limit method of Kaplan-Meier. The log rank test was used to compare survival rates between subgroups of patients. The relative influence of the different variables on survival was studied by multivariate survival analysis using Cox regression.

results

patient demographics at diagnosis (Table 1)

Our file review identified 109 patients aged 80 years or older at diagnosis of NHL. The mean patient age was 83.7 years (range, 80–95 years); 60% were female (65F/44M). The mean duration symptoms before diagnosis was 3.8 months (range 0–36). In eight patients (7%), the lymphoma could not be classified. Stage I disease was recorded in 24%, II in 22%, III in 14%, and IV in 40%. At diagnosis, nodal disease was found in 75% of the patients. Extranodal disease occurred in 77 patients (71%), including 13 patients with disease in multiple extranodal sites. The most frequent site of involvement was the bone marrow (\( r = 26 \)). Twenty-one patients had splenomegaly. Lactic dehydrogenase levels (LDH) were elevated in 50 patients (48%). Serum \( \beta-2 \)-M, measured at diagnosis in 34 patients, was found to be elevated in 29 (85%), and left ventricular ejection fraction, measured in 52 patients at diagnosis, was below 50% in six (11.5%). Forty patients had a poor PS (score 2–4), 52 had an IPI score of 3–5.

aggressive NHL

Seventy-eight patients (72%) had aggressive NHL, 66 (61%) with diffuse large B-cell lymphoma, nine with T-cell lymphoma. Patients with aggressive lymphomas were significantly more likely to have a poor performance status (\( P = 0.05 \)), high LDH (\( P = 0.032 \)), and a high IPI score (\( P = 0.034 \)).

indolent NHL

Twenty-five patients (23%) had indolent NHL, 11 with follicular lymphoma, 10 with small lymphocytic lymphoma and three with MALT lymphoma. Most of them, if treated received mild chemotherapeutic regimens (\( n = 15 \), 62.5%) and only three patients (12.5%) received aggressive treatment.

therapy (Table 2)

Eighteen patients did not receive any form of treatment, including three with indolent lymphomas in whom we followed a watch-and-wait policy, nine patients who refused treatment, and six who died before therapy could be administered. Thirty-seven patients received radiotherapy, 12 as initial treatment and eight as the sole treatment. Initial chemotherapy, administered to 79 patients (72%) consisted of a combined protocol in 62 cases, and oral treatment in 17 cases, as shown
Thirty-two patients received two chemotherapy regimens, and seven patients received three. In 65% of the patients, the intention-to-treat regimen was judged to be adequate. Only 16% of the patients received 100% of the calculated dose; 38% received \( \geq 80\% \) of it, 47% received 50–75% of it. Only half the patients receiving intravenous chemotherapy completed six cycles or more.

Complications were prevalent and occurred in 75% of the patients (88% of aggressive NHL and 53% of indolent NHL). No complications were reported in 62% of patients that did not receive chemotherapy compared to 23% of patients receiving mild chemotherapy and only 15% of patients receiving aggressive chemotherapy \( (P = 0.04) \). Blood cytopenias were common: anemia (Hb < 10 g/dl) in 48%, neutropenia <1000/μl in 49%, and thrombocytopenia <100 000/μl in 29%. Anemia was reported in 33% of patients not receiving chemotherapy, compared to 46% of those receiving mild chemotherapy and 56% of those receiving aggressive chemotherapy. Neutropenia was reported in 38% of patients receiving mild chemotherapy compared to 58% receiving aggressive chemotherapy \( (P = 0.03) \).

Thirty-three patients received granulocyte colony-stimulating factor (G-CSF) support. Sixty-one patients (56%) died, 40% of indolent lymphoma patients and 60% of aggressive lymphoma patients. Sixteen died from sepsis and 29 from NHL. Data on response to treatment were available for 69 patients. The overall response (OR) rate was 84% (complete 56.5%, partial 27.5%).

The OR for patients with aggressive lymphoma was 87% (complete 59%, partial 28%). In low IPI it was 90% (complete 76%, partial 14%), and in high IPI it was 85% (complete 46%, partial 39%). In localized disease (stages I, II) it was 86% (complete 68% partial 18%), and in advance stage disease in was 87% (complete 50%, partial 37%).
The OR for patients with indolent lymphoma was 72% (complete 50%, partial 22%). In localized disease (stages I, II) it was 87% (complete 75% partial 12%), and in advance stage disease in was 60% (complete 30%, partial 30%).

**comparison by age (Table 3)**

On comparison of the patients by age, namely, 80–84 years ($n = 82$) versus 85 years and older ($n = 27$), we found that significantly more patients in the older group had aggressive lymphomas (70.5% versus 92%, $P = 0.033$), elevated LDH levels (42% versus 67%, $P = 0.028$), and IPI scores $\geq 3$ (44% versus 63%, $P = 0.094$). PS was similar. The therapeutic approach also differed significantly. Despite the more aggressive features of the patients in the older group, one-third of them remained untreated, compared with 9% of the younger group. No significant differences were found between the two groups in type of chemotherapy administered, number of chemotherapy cycles, percentage of total dose given, or administration of radiotherapy. In both groups, PS appeared to play a role in the therapeutic decision: 90% of patients with a good PS (0–1) received treatment compared to 76% with a poor PS (>1). The intention to treat regimen was judged adequate as defined in the Methods section, in 72% of the younger group but only 44% of the older group ($P = 0.018$). For patients who underwent treatment, the response rate and median survival were similar in the two groups: 57% of patients in both groups achieved complete remission, and the median survival time was 30 months in the younger patients and 20 months in the older patients ($P = 0.2$).

**survival data (Table 4, Figure 1)**

The overall 3-year survival rate for all 109 patients was 43.3 ± 5%, and the median survival time was 26 ± 6 months. The median follow-up was 33 months (range 1–150).

Patients with indolent lymphomas had a significantly better 3-year survival and median survival than those with aggressive lymphomas (69.9% and 72 months versus 34.9% and 18 months respectively, $P = 0.016$ (Table 4, Figure 1A).

Poor PS and high IPI adversely affected survival. The 3-year survival was 56.9% for patients with PS ≤ 1 and 19.7% for patients with PS ≥ 2; the corresponding median survival times were 65 months and 13 months ($P < 0.0001$) (Figure 1B). Similarly, the 3-year survival was 68.5% for patients with a low-risk IPI (52) compared to 15.6% for a high-risk IPI (≥3), and the median survival was not reached for the low-risk IPI subgroup versus 12 months for the high-risk IPI subgroup ($P < 0.0001$). In patients with aggressive lymphoma the 3-year survival was 69% for patients with a low-risk IPI compared to 7.2% for a high-risk IPI, and the median survival was not reached for the low-risk IPI subgroup vs 10 months for the high-risk IPI subgroup ($P < 0.0001$). In patients with indolent lymphomas the 5-year survival was 74% for patients with a low-risk IPI compared to 34% for a high-risk IPI, and the median survival was not reached for the low-risk IPI subgroup versus 43 months for the high-risk IPI subgroup ($P = 0.03$).

Patients who received treatment regimen that was judged by intention to treat to be adequate, as defined in the Methods section, had a significantly longer median survival than those who received inadequate intention to treat regimen (34 versus 10 months, $P = 0.0032$).

Patients who received ≥80% of the calculated combination chemotherapy dose had a longer median survival (72 versus 20 months) than those who did not, but the difference did not reach statistical significance ($P = 0.18$), probably owing to the three patients who are still alive for more than 100 months.

**predictors of survival**

Multivariate analysis with stepwise Cox regression analysis was performed to examine which parameter (IPI score, PS, intention to treat) best predicted survival. All the parameters were found to contribute to survival, but the IPI score was the most significant ($P < 0.001$), followed by adequacy of intention to treat regimen ($P = 0.004$) and performance status ($P = 0.052$).

Survival analysis for patients with aggressive lymphoma showed that the median survival was not reached in those with stage I disease, and was 11, 46 and 13 months in patients with stages II, III, and IV, respectively ($P = 0.007$). The median survival was 13 months in patients with aggressive lymphoma who did not receive any chemotherapy ($n = 20$), 7 months in those treated with mild chemotherapy ($n = 9$) and 20 months in

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**Table 3. Comparison of NHL patients less or more than 85 years old**

| Age            | Number of pts | Male:Female (M:F) | Histology                  | Stage | IPI score | Received therapy | Intention to treat regimen judged as adequate | Response rate | Complete response | Partial response | No response | 3-year survival | Median survival (months) | Age            | Number of pts | Male:Female (M:F) | Histology                  | Stage | IPI score | Received therapy | Intention to treat regimen judged as adequate | Response rate | Complete response | Partial response | No response | 3-year survival | Median survival (months) |
|----------------|---------------|-------------------|-----------------------------|-------|-----------|------------------|-----------------------------------------------|---------------|-------------------|-------------------|-------------|------------------|----------------------------------------|----------------|---------------|-------------------|-----------------------------|------------------|-------------------|-------------------|-------------|------------------|------------------------|
| 80–84 years    | 82 (75%)      | 1:1.4             | Indolent lymphoma           | I     | 1–2       | Yes              | 56 (72%)                                      | 82%           | 31 (56.5%)        | 14 (25.5%)        | 10 (18%)   | 45.4±6%          | 30±10                    | Age ≥85 years   | 27 (25%)      | 1.1:1             | Aggressive lymphoma         | II    | 3–5       | No               | 56 (72%)                                      | 93%           | 31 (56.5%)        | 14 (25.5%)        | 10 (18%)   | 45.4±6%          | 30±10                    |
those treated with aggressive chemotherapy \( n = 42 \) \( P = 0.05 \), Fig. 1C). On univariate analysis, IPI score, PS, and adequate intention to treat regimen all contributed to survival (Table 4) but on multivariate analysis only IPI score \( P < 0.001 \) and adequate intention to treat regimen \( P = 0.026 \) retained significance in patients with aggressive NHL.

### discussion

The optimal therapeutic approach to elderly lymphoma patients has not been defined, and almost no information is currently available to guide clinicians treating patients older than 80 years. Advanced age is known to be an adverse prognostic factor in all subtypes of NHL [14–20]. In the clinical evaluation of the REAL classification, 1403 patients were analyzed for the effect of age on the characteristics and clinical behavior of NHL [4]. Small lymphocytic lymphoma and lymphoplasmacytoid lymphoma were found to occur more frequently in patients older than 70 years. However, few clinical differences were observed among the age groups, with the exception of a greater frequency of poor PS and bone marrow infiltration in the older patients. Response to treatment, median overall survival, and EFS decreased with age. Complete response rate decreased from 68% in the youngest patients to 45% in the oldest patients \( P < 0.0001 \).

Maartense et al. [20] described 318 patients 75 years or older who were part of a registry of 1167 NHL patients in the Netherlands. Fifty-nine percent of the patients were in an advanced stage of disease. A high IPI score was observed more frequently in the over-70 group, and treatment was more often withheld from patients older than 75 (no treatment 23%, surgery alone 9%, radiotherapy alone 20%). The complete response rates decreased with advancing age to 32% in patients \( \geq 75 \) years old, and overall survival decreased sharply in patients \( > 70 \) years old, with the 5-year survival being only 15% in patients aged 80–85 years and 8% for those above 85 years. Nevertheless, among the anthracycline-treated patients aged 60 years and more, the complete response rate remained unchanged, and complete responders had a good probability of long-term survival.
Another study of NHL in 64 patients aged 70 years or more suggested that elderly patients are more likely to have aggressive disease, a diffuse pathology, and an extranodal presentation [21]. The IPI was a strong predictor of both survival and response. Gomez et al. [18] showed that in patients aged 60–94 years, the risk of mortality related to doxorubicin-based therapy was associated with poor PS rather than with increasing chronologic age.

In the present study, the majority of the lymphomas diagnosed in patients aged 80 years or more were aggressive, mainly diffuse large B-cell lymphomas. The incidence of aggressive lymphomas continued to increase with age, especially in patients aged 85 years and more; very few of the patients in this age group had indolent lymphoma (Table 3) as reported also in the earlier studies [18, 20].

At diagnosis, most of our patients had extranodal disease, and many were in an advanced stage and had a high LDH level, poor PS, and high IPI score. Serum β2-microglobulin levels were elevated in 85% of the patients in whom they were measured. High β2-microglobulin levels are known to be associated with poor prognosis in NHL.

Despite these adverse features, the response rate and complete response rate were high in both the patients with indolent (complete response, 50%) and aggressive (complete response, 59%) lymphomas. However, in the patients with aggressive lymphomas, the median survival time was short (18 months), and the 3-year survival rate was only 35%. In the more elderly patients (≥85 years), although the rates of elevated LDH and high IPI score were significantly higher, those who were treated responded, and achieved the same complete response rate as the patients aged 80–84 years.

On univariate analysis, PS, IPI score and adequate intention to treat regimen were all good predictors of survival. On multivariate analysis, they all retained significance in all NHL patients but in aggressive NHL patients, only IPI score and adequate intention to treat regimen retained significance. Thus, the IPI score is the best prognostic parameter, and in patients with aggressive lymphoma no patient with a high IPI score survived 5 years compared with 70% of those with a low IPI score.

An earlier study reported that survival in elderly patients with NHL is related to achieving a complete response, which in turn is dependent upon the administration of optimal doses of antineoplastic drugs [19]. In our study, a substantial number of the patients with aggressive lymphomas received suboptimal therapy consisting of reduced doses of chemotherapy (62%), fewer than 4 cycles of therapy (33%), non-anthracycline-based regimens (40%), or no chemotherapy whatsoever (28%). This was most apparent in our comparison of patients aged more or less than 85 years (Table 3). Significantly more patients in the older group were left untreated, and significantly fewer of those treated responded, and achieved the same complete response rate as the patients aged 80–84 years.

The inclination to under-treat may be the result of early reports of high rates of treatment-related morbidity and mortality in older patients [14–15]. In 1984, Armitage and Potter [14] reported on 20 patients aged 70–94 years who were treated with full-dose CHOP with a treatment-related mortality of 30%. They therefore recommended altering drug doses in elderly patients.

Figure 1. Kaplan-Meier curve of cumulative overall survival. (A) Patients with indolent (n = 25) versus aggressive lymphoma (n = 78), (B) Patients with performance status score 0–1 (n = 63) versus patients with performance status score ≥2 (n = 40), (C) Patients with aggressive lymphoma who did not receive chemotherapy (n = 20) versus those who received mild chemotherapy (n = 9) and those who received aggressive chemotherapy (n = 42).
Subsequently, however, several groups reported on lower rates of treatment-related mortality for CHOP/CNOP, in the range of 7–13% [7, 17, 18]. Recent trials have shown that with the addition of G-CSF, even dose-density CHOP (biweekly full-dose CHOP) can be safely administered to patients aged 61–75 years, with similar toxicity to standard CHOP and significantly better event-free and overall survival [10]. In this dose density trial the rate of therapy-associated deaths without progression was only 3%.

Co-morbidities also play an important role in aggressive NHL, with survival of those with severe co-morbidities being half that of patients without co-morbidities [22]. Over 60% of patients aged more than 70 years at diagnosis of NHL have one or more serious co-morbidities, and the question of whether the lower survival in this group is due to the co-morbid condition itself, treatment toxicity, or treatment inadequacy remains unresolved.

The therapeutic goal in treating elderly NHL patients is to maintain a balance between effective therapy and treatment toxicity. Guidelines are needed to identify patients who are likely to tolerate and respond to treatment with minimal treatment-related morbidity and mortality. Collaboration with geriatric physicians to develop better methods to assess physiologic reserve and co-morbidity [13] may help clinicians meet this challenge and avoid the denial of curative or life-extending therapy on the basis of age alone.

Because of the retrospective nature of the present study, we could not accurately provide a toxicity profile for each treatment or draw firm conclusions regarding the best treatment approach to very elderly patients with lymphoma. Well designed prospective randomized clinical trials examining various treatment options in the population of patients 80 years and older with concomitant diseases will answer this question.

In the meanwhile, for older patients with asymptomatic advanced-stage low-grade NHL, we recommend a watch-and-wait policy, as researchers have recently shown that the actuarial wait policy, as researchers have recently shown that the actuarial survival of patients treated with chemotherapy for aggressive non-Hodgkin’s lymphomas. Ann Hematol 1999; 78: 315–319.

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