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ORIGINAL ARTICLE

**Frank P.J. Peters · Roy I. Lalisang
Martin M.F. Fickers · Frans L.G. Erdkamp
Jacq A.J.M. Wils · Sjef G.J. Houben · Jaap Wals
Harrie C. Schouten**

Treatment of elderly patients with intermediate- and high-grade non-Hodgkin's lymphoma: a retrospective population-based study

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Abstract *Purpose and methods:* Nowadays more people are becoming older. The median age of a patient with non-Hodgkin's lymphoma (NHL) at diagnosis is over 60 years. The incidence of NHL in elderly has increased in the last decades. Therefore, in the future, NHL will be diagnosed more often in the elderly. Data of all patients in the south-east of the Netherlands with newly diagnosed NHL between January 1991 and January 1995 were analysed in a retrospective multicentre population-based study to investigate if and how elderly patients (>60 years) with advanced NHL (Ann Arbor Staging ≥IIB) of intermediate- and high-grade malignancy were treated. Treatment modalities applied, outcome, and causes of death were evaluated. Treatment was considered inadequate if it deviated from the standard anthracycline-containing chemotherapy (CNOP/CHOP) for a minimum of six cycles. *Results:* The entry criteria were met by 68 patients. Of these patients, 57 (83.8%) were treated and 11 (16.2%) were not treated. The treatment consisted of CHOP (36 patients), CNOP (6 patients), chlorambucil (13 patients), or COP (2 patients). Forty-two of 68 patients had adequate treatment, but 14 of 42 (33.3%) patients had a suboptimal numbers of cycles (<6). Of 28 patients with adequate chemotherapy, only 16 had the optimal number of cycles and dose; the result is that the treatment of 76.5% (52/68) of patients differed from that of their younger counterparts. The most important reason for treatment not being optimal was high age (23%) or poor performance (35%). In the appropriately treated patients, 62.5% (10/16) had a complete response. Survival in the CHOP/CNOP-treated group was better than in other groups. The main cause of death in the total study group was NHL. The results cannot be explained by the different international prognostic index. *Conclusion:* A significant subset (76.5%) of elderly people with intermediate/high-grade NHL received suboptimal therapy, mainly because of a suboptimal performance status. However, a significant part of the patients (23%) were not treated optimally because of high age, despite a good performance. For improving the overall survival in the elderly, it is not only the schedule that is important, but also the intention to treat the elderly patient.

Keywords Elderly · Non-Hodgkin's lymphoma

F.P.J. Peters (✉) · F.L.G. Erdkamp
Maasland Hospital Sittard, Department of Internal Medicine, Hematology and Oncology, Walramstraat 23, 6131 BK Sittard, The Netherlands
e-mail: f.erdkamp@orbisconcern.nl
Fax: +31-46-4597983

F.P.J. Peters · R.I. Lalisang · H.C. Schouten
University Hospital Maastricht, The Netherlands

M.M.F. Fickers
De Wever Hospital Heerlen, The Netherlands

J.A.J.M. Wils
Laurentius Hospital Roermond, The Netherlands

S.G.J. Houben
Sint Jozef Hospital Kerkrade, The Netherlands

J. Wals
St. Gregorius Hospital Brunssum, The Netherlands

Introduction

The incidence of non-Hodgkin's lymphoma (NHL) has increased over the past decade and a further increase can be expected [1, 2]. The median age at diagnosis is over 60 years. Nowadays, 13% of the Dutch population is older than 65 years and this percentage is increasing by 1.3% each year [3]. Therefore, in the future, it is expected that NHL will be diagnosed more often in elderly people.

Elderly people with intermediate- or high-grade NHL have a relatively poor prognosis compared with younger patients. It is important to know which factors contribute to this worse outcome. Some studies concluded that elderly NHL patients have a reduced tolerance for combination chemotherapy [1, 4, 5], that they have a higher co-morbidity [6], were treated with lower doses of chemotherapy [7, 8], and/or that tumour biology vary with

age [9, 10, 11, 12]. However, some studies contradicted these conclusions [6, 7, 8, 9]. Whatever the reason, age is a factor of prognostic significance [1, 5, 6, 7, 11], and is one of the factors in the international prognostic index [13]. On the basis of a large randomised study [24], CHOP is now considered to be the standard therapy owing to its efficacy and relatively limited toxicity. Also in the elderly, this therapy can be given without major problems [23, 24, 25]. In addition, other studies in which less intensive schedules have been used have had a relatively poor outcome [15, 16, 17, 18, 19, 20]. Therefore, CHOP may also be the standard therapy in the elderly.

We performed a retrospective population-based study in elderly people with high- or intermediate-grade non-Hodgkin's lymphoma, to evaluate the fraction of elderly patients treated, which treatment regimens were applied, and what the outcomes of the treatments were.

Patients and methods

The Comprehensive Cancer Centre Limburg (IKL) has a population-based cancer registry serving an area of about 850,000 inhabitants [28]. In this area, between January 1991 and January 1995, 240 patients were diagnosed with a NHL. Because our main focus was the status of systemic therapy, the inclusion criteria for the current study were diagnosis of NHL according to the working formulation groups D, E, F, G, and H, an age of above 60 years, and advanced NHL according to the Ann Arbor staging stage IIB or more [21, 22]. Sixty-eight patients fulfilled these criteria and were enrolled in this retrospective study.

Patients with primary central nervous system lymphoma were excluded (n=6). Treatment modalities applied and results were evaluated by a chart review. Factors influencing the choices of treatment were analysed.

Treatment was considered inadequate if it deviated from standard NHL therapy, which means CHOP (cyclophosphamide, 750 mg/m^2, i.v., day 1; doxorubicin, 50 mg/m^2, i.v., day 1; vincristine, 1.4 mg/m^2, i.v., day 1; prednisone, 100 mg, po, days 1–5) or CNOP (COP as in CHOP and mitoxantrone, 10 mg/m^2, i.v., day 1, instead of doxorubicin). Optimally treated patients were arbitrarily defined as all patients treated with CHOP/CNOP with at least 6 cycles, every 3 or 4 weeks, without dose reductions and/or treatment delay. The remission rates in these patients were evaluated.

Patients without evidence of pathological mass at the physical or radiological examination at the end of the treatment were judged to have complete remission (CR). A partial response (PR) was defined as a 50% reduction in two dimensions in the diameter of the measurable lesions compared with the original size. Patients with progressive or stable disease or less than 50% regression of the tumour were defined as non-responders.

We also evaluated the reasons why patients were not treated according to the policy defined above and the causes of death and survival.

In almost all the patients included, the staging procedures included physical examination, blood cell counts with leukocyte differentiation, blood chemistry, computed tomography of chest and abdomen, bone marrow aspiration, and biopsy.

Kaplan–Meier overall survival curves were constructed to approximate the life expectancy of the treatment populations [27].

The mean international prognostic index (IPI) was calculated for every treatment group (Table 1). Significance was measured by the Breslow statistical analysis method. A P value of 0.05 (two-sided) was considered to be the limit of significance.

Table 1 International Prognostic Index (*IPI*) of the different groups

Treatment group	No. of patients	IPI
CHOP/CNOP	42	2.33
No CHOP/CNOP	26	2.19
Chlorambucil	13	1.92
Chlorambucil/COP	15	1.93
No chemotherapy	11	2.55

Results

The main characteristics of the patient population are listed in Table 2 and Fig. 1. Initially, 57 (83.8%) of the 68 patients were treated, but with various chemotherapy regimens, and 11 (16.2%) were not treated with chemotherapy.

The treatment consisted of CHOP (36 patients), CNOP (6 patients), chlorambucil (13 patients), or COP (CHOP without doxorubicin; 2 patients). CHOP or CNOP therapy was used for 23 of the 26 patients (88%) in the age category of 60–70 years and for 19 of the 42 (45%) patients in the age category of above 70 years. In the 70 years or below age category, 9 out of 23 (39%)

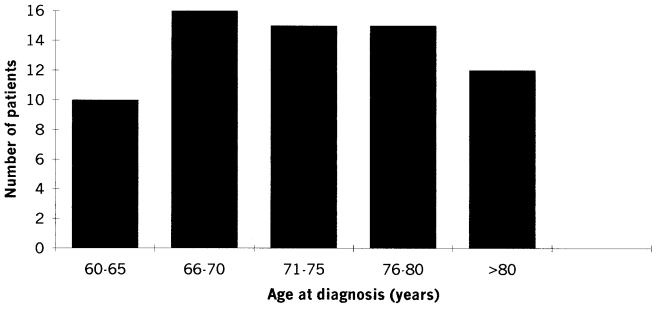

Fig. 1 Age distribution of the 68 patients with non-Hodgkin's lymphoma who participated in this study

Table 2 Characteristics of the NHL patients participating in this study [total number of elderly NHL patients in IKL region 240; number fulfilling study entry criteria 68; median age 74 years, range 61–92 years)]

Characteristic	Number of patients (n=68)
Gender	
Male	30
Female	38
Stage (Ann Arbor)	
IIB	6
III	12
IV	38
≥IIB (incomplete staging)	12
B symptoms	35
Therapy	
CHOP	36
CNOP	6
Chlorambucil	13
COP	2
No chemotherapy	11

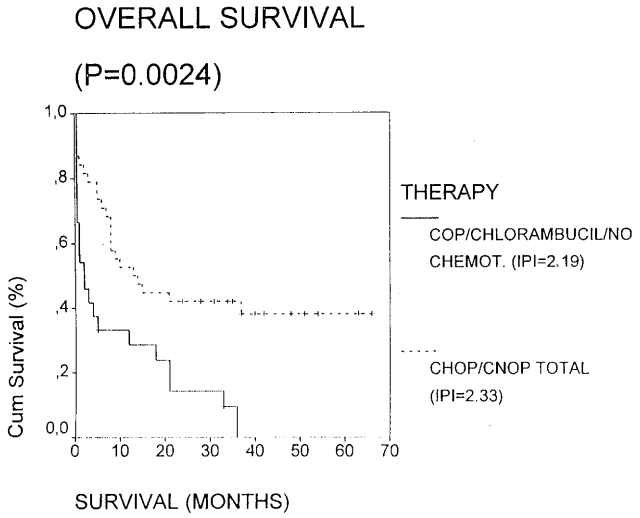

Fig. 2 Overall survival of the total CHOP/CNOP group vs the COP/chlorambucil/no chemotherapy group

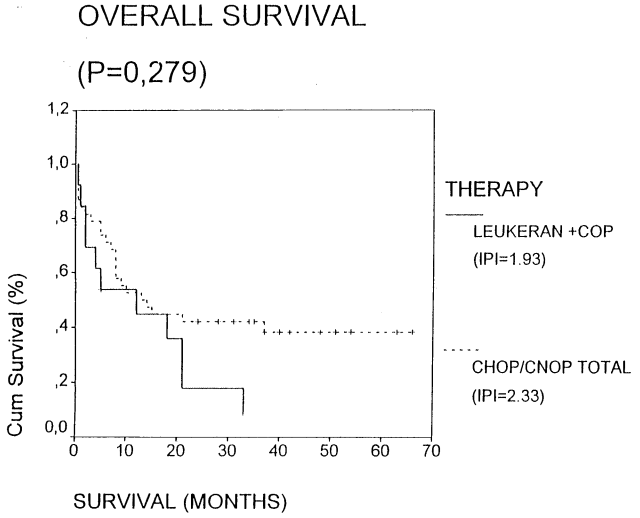

Fig. 3 Overall survival of the chlorambucil/COP group vs the CHOP/CNOP total

patients had the optimal number of cycles and dose, and the complete remission rate was 67% (6 of 9 patients). In the above 70 years of age category, 7 out of 19 patients (37%) had the optimal number of cycles and dose, and the complete remission rate was 57% (4 of 7 patients). In total, with CHOP or CNOP considered as adequate therapy, 42 of these 68 patients were treated appropriately. However, 14 of these 42 patients (33.3%) received a suboptimal number of cycles (less than six cycles). Only 16 of the 42 patients treated with CHOP/CNOP had an optimal number of cycles and dose; this means that 52 out of 68 patients (76.5%) were treated in a way different from our pre-defined optimal therapy.

Of the 16 patients receiving an optimal treatment, 10 (62.5%) reached a complete response. The Kaplan–Meier curves of the patients who were treated with CHOP/CNOP and of the patients receiving no CHOP/CNOP or other chemotherapy showed significant survival differences in favour of the CHOP/CNOP group, although the IPI in the CHOP/CNOP group was higher than in the other group (P=0.0024) (Fig. 2). Nevertheless, when the survival of the CHOP/CNOP group (optimal and suboptimal) was compared with that of patients in the COP/chlorambucil group, there was no significant survival difference (P=0.279) (Fig. 3). However, the IPI in the COP/chlorambucil group was much better than in the CHOP/CNOP group (1.93 vs 2.33). The most important reason for not being treated with CHOP or CNOP was high age (without a poor performance status) (6 out of 26 patients=23%) and poor performance status, above WHO 1 (9 out of 26 patients=35%). Other reasons are death before start of therapy, initially wrong diagnosis, thrombocytopenia, cardiac causes, and patient's choice (Table 3). Most of the patients who died, died of NHL (32/53=60%). More people in the CHOP/CNOP group than in the other groups died of therapy-related toxicity (10%) (Table 4). Eighteen of the 42 patients (43%) in the CHOP/CNOP group and 14 out of 26 patients (54%) in the other groups died from progressive NHL. However, at the end of our study, a significant proportion (14 of 42, 33%) of the CHOP/CNOP-treated patients was still alive, in contrast to only one out of the 26 patients (4%) in the other groups.

In the other groups, six patients died of causes not related to the NHL or NHL treatment, namely sepsis without neutropenia (n=2), pneumonia without neutropenia (n=1), metastatic rectal carcinoma (n=1), and bleeding without thrombocytopenia (n=2).

Table 3 Reasons for elderly NHL patients not being treated with CHOP or CNOP therapy

Reason	No. of patients
Poor performance (WHO ≥2)	9
Too old (performance WHO ≤1)	6
Died before treatment	4
Initial incorrect diagnosis	1
Thrombocytopenia	1
Cardiac (performance 1)	1
Patient's choice	2
Unknown	2
Total	26

Table 4 Causes of death in the CHOP/CNOP group and the other groups

	Reason	CHOP/CNOP group (proportion of patients)	Other groups (proportion of patients)
Died	NHL	18 (43%)	14 (54%)
	Other reason	3 (7%)	6 (23%)
	Therapy-related	5 (12%)	0
	Unknown	2 (5%)	5 (19%)
Alive		14 (33%)	1 (4%)
Total		42	26

Discussion

This study was based on the hypothesis that the poor outcome seen in elderly patients with high- or intermediate-grade NHL is in part due to undertreatment of these patients [31]. In our study we indeed observed that 76% of the patients were not treated optimally and that a significant subset (9/26=35%) of elderly NHL patients received no CHOP or CNOP therapy, mainly because of a suboptimal performance status. Also, a significant part of these patients (23%) were not treated optimally because of their high age, although they had a good performance status.

Survival in the CHOP/CNOP group was better than in the no CHOP/CNOP group although the IPI was higher in the CHOP/CNOP group. Nevertheless, there was no significant survival benefit in the CHOP/CNOP group when compared with the chlorambucil/COP group.

However, the IPI score in the CHOP/CNOP group was higher than in the COP/chlorambucil group. This suggests that, for the same IPI score, the survival is better in the CHOP/CNOP group than in the COP/chlorambucil group.

There is no survival benefit of complete CHOP/CNOP (six or more cycles without dose reduction or interval prolongation) over incomplete CHOP/CNOP. The explanation for this observation is that the incomplete CHOP/CNOP group included ten patients who underwent six or more cycles and had one dose reduction and two patients who underwent six or more cycles and had one interval prolongation. In this population of 12 patients, who were treated nearly completely, the mean survival time was 32 months. These relatively long survival times in the nearly optimally treated patients do not differ significantly from that of the optimally treated patients.

The present study demonstrates that a 3–4 week CHOP/CNOP schedule in elderly NHL patients is associated with a CR of 60% and a 3-year overall survival rate of 44% (not shown); this is comparable to the results of an unselected group of adult patients undergoing three weekly CHOP treatments (CR=44%), with a 3-year survival rate of 54% [24].

These results are comparable with those of Sonneveld et al., who found a CR of 49% and an overall survival rate of 41% in elderly NHL patients treated with a 4-week schedule of CHOP [23]. In patients who reached CR, the prospect of remaining in CR is relatively high (54%) [24]. With standard doses of CHOP, the frequency of death not related to lymphoma might be higher in older patients. However, D'Amore and Ansell who have adjusted for these deaths still find an excess of deaths due to lymphoma [1, 18]. The present study also showed that death in the majority of the patients studied was caused by NHL (32 of 51 patients= 63%). As reported by Gomez et al., the risk of death in elderly NHL patients treated with doxyrubicin-based chemotherapy is associated with poor performance status and is not related to increasing chronological age [29]. It therefore suggests that elderly patients with a good performance status are candidates for doxorubicin-based therapy, the gold standard at the moment [23, 24]. Important is the intention to treat the elderly NHL patients and to emphasise the importance of dose intensity. When CHOP doses were decreased because of advanced age of the patients, the complete remission rate decreased and the survival diminished [7, 20].

Table 5 Life expectation for people of various ages in the United Kingdom (1994; according to Khaw [32])

Age (years)	Life expectation (years)	
	Males	Females
60	19.7	23.6
65	15.4	19.0
75	9.0	11.5
85	4.9	6.3

It has become evident that intermediate- and high-grade NHL can be cured. The gold standard in younger patients is CHOP [24]. In elderly patients with aggressive non-Hodgkin's lymphoma CHOP/CNOP is well tolerated [9, 23].

Therapy-related (CHOP/CNOP) death was observed in five patients (12%=5/42). It was caused by decompensatio cordis (n=2), *Escherichia coli* sepsis and granulopenia (n=1), pneumonia and granulopenia (n=1), and candida sepsis and granulopenia (n=1). These results are in agreement with those of Sonneveld et al. [23] and Vose et al. [6], who found15% (22/148) and 7% (8/112) treatment-related deaths.

Like Armitage and Gomez we found that more elderly people are susceptible to the toxic effects of chemotherapy and that there are more treatment-related deaths in this group [26, 30]. Although more people in the CHOP/CNOP group died of therapy-related toxicity, we think it is acceptable to treat these older NHL patients with this more toxic regimen if the goal of the treatment is to cure and to prolong survival. However, specific attention should be paid to infection prevention and supportive care.

According to Khaw, the life expectancy decreases with age. However, it is defendable to treat elderly NHL patients, because in every age category the life expectancy is still a few years (Table 5). So treatment of NHL patients in the elderly age category could be beneficial for the individual.

It should be noted that four patients died before starting therapy. Two patients died of gastrointestinal tract bleeding (duodenal ulcers), one patient died of myocardial infarction, and one patient died of sepsis. These results are comparable with those of Vose et al. who found a decreased overall survival in elderly people in addition to deaths due to apparently unrelated causes [6].

In conclusion, this report suggests that the survival rates of elderly NHL patients treated with CHOP/CNOP chemotherapy is better than that of elderly NHL patients not treated with CNOP/CHOP therapy.

In this population-based study a significant population of elderly NHL patients with a good performance

status was not treated with CHOP/CNOP chemotherapy, the gold standard at this moment. Attention should be paid to this fact if treatment results are to be improved.

Remarkable was that 76.5% of the NHL population was treated differently from their younger counterparts. When patients are treated like younger NHL patients, the complete remission ratio and the overall survival are in the same range as that of the younger group in this retrospective population-based study. Prospective trials are needed to prove this conclusion.

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