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ORIGINAL ARTICLE

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The effect of optimal treatment on elderly patients with aggressive non-Hodgkin's lymphoma: more patients treated with unaffected response rates

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Abstract A substantial part of elderly patients (with good performance) with intermediate or high-grade non-Hodgkin's lymphoma (NHL) are not treated with the standard chemotherapy of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). If NHL patients are not treated with CHOP, the outcome is inferior. By adding granulocyte colony-stimulating factor (G-CSF) to CHOP chemotherapy, we aimed at treating more patients with less toxicity. We performed a multicenter population-based study (in the southeast of the Netherlands) in which elderly patients (≥60 years) with intermediate or high-grade stage ≥IIB NHL were treated with CHOP chemotherapy and growth factor G-CSF to increase the number of patients treated according to standard protocols. We also evaluated elderly NHL patients who were not treated with CHOP chemotherapy. Adequate therapy was defined as ≥ six cycles or a total of five cycles when complete remission was achieved after three cycles. Seventy-nine NHL patients fulfilled the selection criteria. The patients were treated with CHOP plus G-CSF (*n*=46), CHOP (*n*=19), cyclophosphamide, vincristine, and prednisone (COP) (*n*=2), chlorambucil and prednisone (*n*=2), or prednisone (*n*=1). Nine patients were not treated with chemotherapy. The median age was 72 years (60–87). Of the 79 NHL patients, 65 were treated with CHOP chemotherapy (82%); 38 of 65 patients (59%) were adequately treated. The complete remission rate in the NHL group treated with CHOP was 65% (42 of 65 patients). The overall 3-year survival was 50%. Most of the patients died from progressive NHL (53% in the CHOP and 77% in the group not treated with CHOP). The treatment-related mortality was 15% in the CHOP group. The most important reason for not treating patients with CHOP (with or without G-CSF) was poor performance (WHO ≥2). A significant subset of patients can be treated with CHOP chemotherapy with acceptable toxicity. The combination of CHOP plus G-CSF increased the absolute number of treatable elderly patients, resulting in more (absolute) patients with complete remission and overall survival compared to our previous study.

Keywords Aggressive non-Hodgkin's lymphoma · Chemotherapy treatment · Elderly patients

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Introduction

Prognosis of aggressive non-Hodgkin's lymphoma (NHL) in the elderly is poor. One possible reason for this poor outcome is that elderly patients tolerate chemotherapy less well than young patients do. The potentially higher toxicity may be attributable to changes inherent in aging such as diminished response of the hematopoietic system after chemotherapy, changes in body composition leading to altered drug distribution, decreased liver metabolism affecting drug metabolism, and reduced kidney function leading to decreased clearance of the cytostatic drug, which may lead to a higher exposure to the drug [1].

Elderly patients with aggressive non-Hodgkin's lymphoma are believed to be incapable of receiving full-dose CHOP chemotherapy. However, standard CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, and prednisone) is still the gold standard [2, 11, 19, 20].

In a previous study of our group, we found that a significant subset of elderly patients (76%) with aggressive

NHL was treated with nonstandard schedules [3]. Also, only 16 of 42 (38%) patients treated with standard chemotherapy received a full dose and optimal numbers of cycles.

Other studies showed that elderly patients who were treated with nonstandard schedules (or dose reduction or interval prolongation) had lower remission rates and decreased survival [4, 5].

We conducted a multicenter population-based study in which elderly patients with intermediate or high-grade NHL were treated with CHOP and growth factor G-CSF to increase the number of patients treated according to standard protocols and thus to improve the outcome.

Material and methods

The Comprehensive Cancer Center Limburg (IKL) serves an area of about 850,000 inhabitants. From July 1995 through December 1999, all elderly NHL patients in this area were registered if aged ≥60 years with newly diagnosed, biopsy-proven, Ann Arbor staged ≥IIB [6], intermediate or high-grade (according to the working formulation groups D, E, F, G, H) NHL.

Patients were excluded if they had any of the following: previous treatment with radiotherapy or chemotherapy, low-grade lymphoma, overt central nervous system disease, symptomatic cardiac complaints, a life expectancy <3 months, creatinine clearance of <60 ml/min, and serum bilirubin more than twice the upper value.

All patients who fulfilled the inclusion criteria were registered at the IKL and followed until death or until December 1999. The patients were treated with CHOP (cyclophosphamide 750 mg/m^2 i.v. on day 1, doxorubicin 50 mg/m^2 i.v. on day 1, vincristine 1.4 mg/m^2 i.v. on day 1, prednisone 100 mg orally on days 1–5) and filgrastim 300 (≤75 kg) or 480 (>75 kg) µg/day subcutaneously on days 2–11. If the elderly NHL patients were not treated with CHOP and G-CSF, the physicians had to report these patients giving the reason for not treating with CHOP plus G- CSF. Based on the data available in the cancer registry (which comprises all of the cancer patients in our area), we could check if all cases of elderly NHL meeting the above-mentioned criteria had been reported. Furthermore, in our region, a central group of pathologists always reevaluate and register all pathology material from all NHL patients. According to this pathology registration system, we also found that no patient was missed.

In patients with hematologic toxicity (leukocytes <3×10^9 and thrombocytes <100×1^9) based on the blood count performed on the 1st day of the next course, modification of the schedule was performed (1 week delay). After three courses, restaging was performed by CT scan of the thorax and abdomen, and if at the time of diagnosis bone marrow was infiltrated by lymphoma cells, a bone marrow aspiration and biopsy was repeated. The patient was treated until complete remission plus two consolidation courses up to a maximum of eight courses. Adequate therapy was defined as ≥ six cycles or a total of five cycles when complete remission was achieved after three cycles (with optimal dose and schedule). Every treatment delay and dose reduction of CHOP chemotherapy made a treatment inadequate.

After completion of therapy again, an evaluation was made by CT scans of the chest and abdomen. Follow-up included monitoring new symptoms and disease progression. Treatment was defined as complete response (CR) (without evidence of disease by radiological examination), partial response (PR) (reduction of disease by 50% in diameter in two dimensions compared to the original size of the tumor), stable disease (less than 50% regression of tumor), or progressive disease (recurrence in originally involved sites or involvement of new sites). Furthermore, we evaluated the causes of death. A Kaplan-Meier curve was constructed to estimate survival [7]. For characterization of the patients, the age-adjusted international prognostic index (IPI) was used [8].

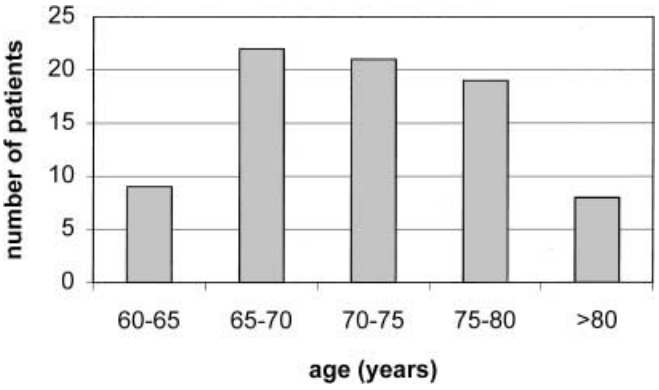

Fig. 1 Age distribution of the patients entered in the study

Table 1 Characteristics of the 79 (44 female, 35 male) NHL patients with a median age of 72 years (range: 60–87). Median IPI=2.0, mean IPI=2.33

Stage	Patients (*n*)
IIB	23
III	13
IV	34
≥IIB	9
Total	79
B symptoms	46

Results

A total of 79 NHL patients were seen in our region who fulfilled all selection criteria. The patients were treated with CHOP plus G-CSF (*n*=46), CHOP (*n*=19), COP (*n*=2), chlorambucil and prednisone (*n*=2), and prednisone (*n*=1), and 9 patients were not treated with chemotherapy. The median age of these 79 patients was 72 years (60–87) with a mean age-adjusted IPI of 2.33 (median: 2.0). Figure 1 shows the age distribution of the whole NHL group. Table 1 shows the patients' characteristics.

Of the 79 patients, 65 patients were treated with CHOP (with or without G-CSF) chemotherapy (82%), and 38 of these 65 patients (59%) were completely treated according to protocol (≥ five cycles without dose reduction or interval prolongation). The complete remission rate in all NHL therapy groups was 53% (42 of 79 patients) and in the group treated with CHOP therapy 65% (42 of 65 patients) (Table 2).

The 3-year overall survival in the CHOP group was 50% (Fig. 2). The reasons for death are summarized in Table 3. At the end of the study, a substantial part of the patients was still alive (46%). Most of the patients died from progressive NHL: 53% in the group treated with CHOP (16 of 30 patients) and 77% in the group not treated with CHOP (10 of 13 patients). Nearly all patients (13 of 14) who had not been treated with CHOP chemotherapy died (Table 4).

Treatment-related mortality in the CHOP group was 15% (10 of 65 patients). Cardiac and infectious complications induced by the chemotherapy were the reasons for treatment-related death (Table 5). Patients treated

Table 2 Treatment results in elderly NHL patients

	Patients (*n*)	Complete CHOP[a]	Complete remission	Reason for no CHOP therapy
CHOP therapy	65/79 (82%)	38 (38/65=59%)	42 (42/65=65%)	
No CHOP	14			
COP	2			Cardiac (*n*=2)
Prednisone and chlorambucil	2			Performance (WHO≥2)(*n*=2)
Prednisone	1			Patient refused
No chemotherapy	9			WHO≥2 (*n*=5)
				Patient refused (*n*=3)
				Died before start of any therapy (*n*=1)

[a] ≥5 cycles without dose reduction or interval prolongation

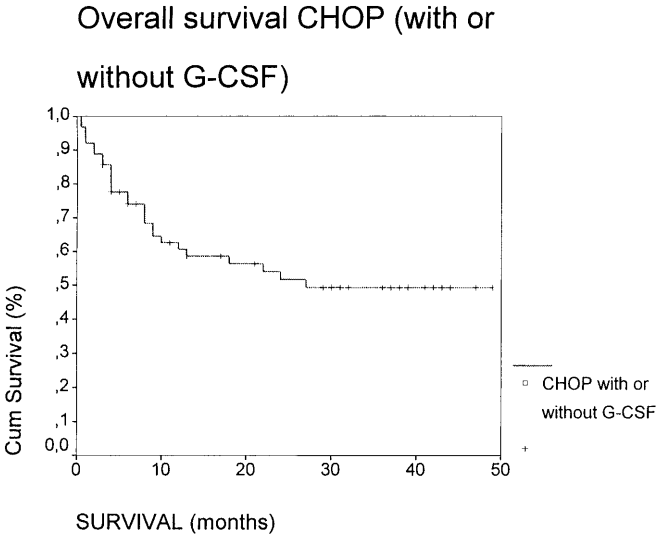

Fig. 2 Overall survival in patients treated with CHOP with and without G.CSF

Table 3 Cause of death in the NHL group (*CVA* cerebrovascular accident)

Cause of death	Patients (*n*)
NHL	26
Cardiac	7
Sepsis with neutropenia	3
Unknown	3
Pneumonia with neutropenia	1
CVA	1
Gastrointestinal bleeding	1
Organic psycho-syndrome	1
Total	43

with G-CSF tolerated it well, and the only significant side effect apparently related to G-CSF was bone pain (8%). The most important reason (7 of 14 patients) for not treating with CHOP with or without G-CSF was poor performance status (WHO ≥2). Four patients refused CHOP chemotherapy (Table 2).

Table 4 Cause of death in the CHOP and no CHOP groups

Cause of death (*n*=14)	CHOP group	No CHOP group (*n*=65)
NHL	16 (25%)	10 (71%)
Cardiac	6 (9%)	1 (7%)
Sepsis and neutropenia	3 (5%)	
Unknown	2 (3%)	
Pneumonia and neutropenia	1 (2%)	
CVA	1 (2%)	
Organic psycho-syndrome	1 (2%)	
Gastrointestinal bleeding		1 (7%)
Unknown		1 (7%)

Table 5 Mortality rate related to CHOP treatment

Cause of death	Patients (*n*)
Cardiac	6
Sepsis and neutropenia	3
Pneumonia and neutropenia	1
Total	10 (10/65=15%)

Discussion

This study was based on the hypothesis that poor outcome seen in elderly patients with aggressive NHL is due to inadequate treatment. By adding G-CSF, we aimed at treating more patients with less toxicity. However, the toxicity issue was not an aspect of this study.

It is known that high-dose intensities even in elderly NHL patients can lead to CR and cure [9, 10, 18]. One of the main toxicities is chemotherapy-induced neutropenia and infection [11]. Therefore, G-CSF may be valuable in reducing these toxicities and potentially leading to a higher number of patients being treated with CHOP chemotherapy and a higher dose intensity of CHOP. G-CSF can reduce dose-limiting neutropenia of chemotherapy in NHL patients [12]. The intention to decrease the toxicity of CHOP chemotherapy with G-CSF could be the reason for doctors to give more patients CHOP treatment.

When we analyzed the whole NHL population, we saw that 82% (65 of 79) of the patients were treated with CHOP chemotherapy (with or without G-CSF) and 59% with the prescribed doses and number of cycles.

In a previous retrospective study of our group, we found that only 62% (42 of 68) of the patients were treated with CHOP-like regimens. However, a substantial part of the patients with good performance status and low IPI were not treated with CHOP chemotherapy [3].

This study shows complete treatment in 59% (38 of 65) of the patients, resulting in a complete remission of 51% (33 of 65) in patients treated with adequate CHOP chemotherapy. In younger NHL populations, nearly the same CR rates have been found [2, 17].

Thus, more patients could be treated with the golden standard chemotherapy of CHOP, resulting in more patients receiving complete treatment and in an absolutely higher number of CR in patients. This suggests that we could change the attitude of the doctor to give more elderly patients CHOP. However, this study contains no information on whether G-CSF is really necessary to give during 3 weeks of CHOP in old patients. Most patients not treated with CHOP had a WHO performance status of ≥2 or refused chemotherapy. All patients with a performance status <2 were treated with CHOP.

In this study age alone was no longer the reason for excluding the patient from CHOP therapy. In our previous retrospective study, we saw that a substantial part of the patients were not treated with CHOP only because of their high age although they had a good performance status [3].

The 3-year survival in patients treated with CHOP (with or without G-CSF) was 50% and is comparable with younger patients treated with CHOP alone [2]. The only clinically important toxicity of G-CSF was bone pain, which was also reported by Yoshiba et al. [14].

Zagonel et al. [15] studied in a randomized trial the effect and the financial consequences of G-CSF in elderly NHL patients treated with cyclophosphamide, doxorubicin, teniposide (Vm-26), prednisone, vincristine, and bleomycin (CHVmP-VB). They observed a higher dose intensity, lower infectious complications (like in our study), and less hospitalization days in the G-CSF group compared to the results in the literature. Although the patient groups in their randomized trial were very small (12 patients treated with chemotherapy plus G-CSF vs 11 patients treated with chemotherapy alone), the authors concluded that prophylactic therapy with G-CSF could result in a cost benefit in older patients with NHL treated with combination chemotherapy [15]. Larger randomized studies are necessary to confirm this conclusion in patients treated with CHOP chemotherapy.

In this study, we observed a treatment-related mortality in the CHOP (with or without G-CSF) group of 15%, which was nearly equal to patients treated with CHOP alone reported by Gomez (10%) [16] and Sonneveld (15%) [13].

Recently, Gomez reported that in elderly patients with NHL, treated with doxorubicin-based chemotherapy, the risk for treatment-related death is only associated with poor performance status (WHO 2–4) [16]. We found in seven of the ten patients who died (therapy related) a performance status at entry of ≥2. Thus, this could be an argument to treat only patients with good performance to decrease the treatment-related deaths (WHO≤1). However, there is a risk that this regimen could lead to undertreatment of patients. Tirelli and Meyer treated elderly NHL patients with a performance status of ≤3 with an acceptable number of toxic deaths [10, 17].

In conclusion, it was not our aim to demonstrate a higher efficacy of G-CSF. It was the intention to make the treatment safer and available to more patients. This study demonstrates that we have succeeded in our goal to treat more patients. By giving attention to the problem of the elderly patients and having designed a regional protocol, we were able to treat more patients without major accidents. The general feeling of physicians may have to be changed based on our results.

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