

Biological and clinical features of non-Hodgkin's lymphoma in the elderly

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Summary

Purpose: The incidence of non-Hodgkin's lymphomas (NHLs) in elderly people has increased in recent years because the world population is getting older. The aim of this study was to compare the biological and clinical features in patients diagnosed with NHLs younger and older than 65 years, and the possible influence of age on the choice of optimal therapeutic approach.

Methods: We retrospectively evaluated 193 patients with NHLs: 111 (68%) were <65 years and 82 (42%) ≥65 years. The following parameters were analysed: age, gender, clinical stage, International Prognostic Index (IPI), histological type, presence of B symptoms, disease localization, presence of bulky mass, Karnofsky performance status (PS), comorbidities, blood counts, liver and renal function and serum LDH.

Results: Elderly patients had statistically more frequent indolent NHLs ($p=0.036$), IPI 3 and 4 ($p<0.0001$), presence of comorbidities ($p<0.001$), and less frequent presence of bulky disease ($p=0.043$). Response to therapy was different in the 2 age groups: 29% of patients ≥65 years achieved

complete remission (CR) in contrast to 71% of patients <65 years ($p<0.001$). The most frequent cause of death was disease progression (PD) (86% of younger patients and 71% of elderly patients ($p=0.150$). Older patients died more frequently because of comorbidities compared younger ones (21 and 10%, respectively; $p=0.250$), and had more complications of therapy (8.1 and 4%, respectively ($p=0.320$). Overall survival (OS) was shorter in older patients in all lymphoma types: indolent lymphoma (36 vs. 17 months), aggressive (22 vs. 20 months) and very aggressive (14 vs. 1 months). Multivariate analysis showed that parameters for shorter survival in the elderly were Karnofsky PS <60, increased serum LDH and treatment toxicity.

Conclusion: In elderly NHLs patients, treatment response and survival are significantly poorer. Since older patients mostly died of PD, they should be treated with standard regimens and best supportive measures.

Key words: clinicopathological features, elderly patients, non-Hodgkin lymphoma, prognosis, response to therapy, survival

Introduction

NHLs are a heterogeneous group of lymphoproliferative disorders of B lymphocytes, T lymphocytes or natural killer (NK) lymphocytes. B cell lymphoma accounts for 80-90% of the NHL cases, with 15-20% being T-cell lymphomas, while NK lymphomas are very rare [1].

NHLs are the 5th leading type of new cancer cases among men and women, accounting for 4-5% of new cancer cases in the United States [1]. According to the 2004-2008 Surveillance, Epidemiology and End Re-

sults (SEER) databases, the annual age-adjusted incidence rate for NHLs was 19.8 per 100.000, while the median age at diagnosis was 66 years [2]. However, as life expectancy increases, people over 65 years are becoming the fastest growing portion of the human population worldwide. Approximately 45.7% of patients diagnosed with NHLs are < 65 years old and the remaining (54.3%) > 65 years (so called "elderly" patients). Definitions of "elderly" patients are numerous and somewhat arbitrary. One of the generally accepted definitions is the one by Coiffier where "elderly" patients are defined as patients who "need treatment

modification, most commonly the boundary is 65 or 70 years” [3].

Elderly patients are more frequently diagnosed with lymphocytic/lymphoplasmacytic lymphoma, diffuse large B cell lymphoma (DLBCL) and peripheral T cell lymphoma [4]. Clinical presentation and prognostic parameters are identical to those described in younger patients [4]. However, there is a tendency for more common extranodal localization than in younger patients, particularly in the gastrointestinal tract, brain, skin and testicles [5-7]. Although the overall incidence of primary extranodal NHLs does not increase with age, these lymphomas are seen primarily in patients older than 60 years [8]. Response rate is usually lower in elderly patients compared with younger ones [4]. In addition, multiple factors complicate and confound treatment and disease outcomes in elderly patients: poor PS, comorbidities (particularly decreased cardiac and renal function), usage of multiple medications. Patients older than 65 years of age are very often treated with alternative, less toxic chemotherapy. Therefore, in light of the general increase in the geriatric population, there is a need for development and validation of treatment strategies for NHLs in the elderly.

The objective of this study was to search for possible differences in biological and clinical characteristics of NHL in younger and older patients and see for possible influence of age on the choice of optimal therapeutic approach.

Methods

Patients

In this retrospective study we studied 193 patients admitted at the Medical Center “Bezanijska kosa”, Belgrade, and diagnosed with NHLs between 2000-2007.

The following parameters were recorded at the time of diagnosis: age, sex, clinical stage, presence of B symptoms, disease localization, presence of bulky mass, Karnofsky PS, blood counts, liver and renal function, and serum LDH. Staging was done according to Ann Arbor classification system [9].

Histological NHL type was performed according to the REAL classification system criteria and histological grade according to Working Formulation classification (WHO) [10,11]. Disease localization was defined as nodal or extranodal (i.e. bone marrow, stomach, skin and central nervous system). IPI was determined for each patient, and defined as low risk (0), medium-low risk (1 and 2), high-intermediate risk (3) and high risk (4 and 5). Comorbidity was defined as the presence of significant cardiovascular (cardiac arrhythmia, myocardial infarction, coronary disease, congestive heart failure, EF \leq 50%), respiratory (dyspnea at test or need for oxygen therapy), urogenital system (serum creatinine $>$ 2 mg/dl, dialysis, transplantation), liver failure (cirrhosis, fibrosis, BUN $>$ 1.5 \times upper limit of normal (ULN), AST/ALT $>$ 2.5 \times ULN) and any other cancer

at the time of diagnosis of NHL [12]. Patients with human immunodeficiency virus positivity were excluded from the study. This study complied with the Declaration of Helsinki and its current amendments and was conducted in accordance with Good Clinical Practice Guidelines. The study was approved by the Institutional Ethical Committee.

Treatment

The patients were treated according to the national guidelines considering histological characteristics of NHL, patient age, presence and number of comorbidities, Karnofsky PS and clinical stage (CS). Different treatment modalities were used: (immuno) chemotherapy, radiotherapy and surgery. Complications of therapy were considered to be hematological (neutropenia, thrombocytopenia, anemia) and others (cardiac, hepatorenal, pulmonary, neurological). Treatment response was evaluated according to International Workshop criteria [13]. The reasons of death were classified as: death from any reason, death due to lymphoma and death due to complications of therapy.

Treatment efficacy was evaluated by its final outcome: CR, fatal outcome and 5-year OS. Therapeutic response was evaluated one month after the last chemotherapy cycle and every 3 months during the first 2 years of follow up, and then 6 months during further follow up.

Statistical analysis

Data were summarized by frequency and percentage for categorical variables. For continuous variables, the median and range were computed. Statistical tests were 2-sided at the 5% level of significance. Univariate analysis was performed to investigate the association between continuous variables and categorical variables using the nonparametric Wilcoxon rank-sum test or the Kruskal-Wallis rank-sum test. OS was defined as the time from the date of the lymphoma diagnosis until death from any cause, and observation ended at the time of the last contact with the patients last known to be alive. Survival curves were plotted by the Kaplan-Meier method; differences between curves were analyzed by the log-rank test. Multivariate analysis for CR and survival was performed by using a logistic regression model. Statistical analyses were performed by using the statistical package SPSS (version 11.5 for Windows).

Results

Patient characteristics

The incidence of NHLs during the study period (January 2000 - December 2007) showed an upward trend irrespective of age. At the time of hospitalization, the average age of the whole group of patients was 59.96 ± 13.36 years (women 61.69 ± 12.45 , men 58.58 ± 13.95 years, $p=0.108$). There were 111 (57.5%) patients $<$ 65 years and 82 (42.5%) \geq 65 years ($p=0.037$). The average age of patients $<$ 65 years was 51.7 ± 10.2 years and of patients \geq 65 it was 70.78 ± 3.5 years.

No statistically significant differences were noted regarding gender, tumor localization (nodal vs. extranodal), stage, histological grade, LDH, Karnofsky PS

and presence of B symptoms. However, aggressiveness of the lymphoma, IPI, presence of bulky disease and presence of comorbidity showed significant differences between younger and older NHL patients (Table 1).

Namely, older patients had statistically more frequently indolent lymphoma, higher IPI and presence of comorbidity, as well as fewer cases of bulky disease.

The most frequent histologic type in both age

Table 1. Clinical characteristics of patients with NHL: comparison of patients < 65 years and patients ≥65 years of age

Characteristics	Total		p-value	<65 years		>65 years		p-value
	N	%		N	%	N	%	
Number of patients	193	100		111	57.5	82	42.5	0.037
Gender			0.131					0.471
Male	107	55.4		64	57.6	43	52.4	
Female	86	44.6		47	42.4	39	47.6	
Localization			0.008					0.581
Nodal	115	59.6		68	61.3	47	57.3	
Extranodal	78	40.4		43	38.7	35	42.7	
Clinical stage			0.0001					0.153
I	19	9.8		13	11.7	6	7.3	
II	45	23.3		31	27.9	14	17.1	
III	19	9.8		11	9.9	8	9.8	
IV	110	57.1		56	5.5	54	65.9	
Grade			0.0001					0.050
Low	101	52.3		51	45.9	50	61.0	
Intermediate	80	41.5		51	45.9	29	35.4	
High	12	6.2		9	8.1	3	3.7	
IPI			0.0001					0.0001
0,1	77	41.18		61	56.5	16	20.3	
2	38	20.32		23	21.3	15	19	
3	56	29.95		20	18.5	36	45.6	
4	16	8.56		4	3.7	12	15.2	
LDH			0.001					0.094
Above normal	73	37.8		44	39.6	29	35.4	
Normal	120	62.2		67	60.4	53	64.6	
Bulky disease			0.0001					0.043
Yes	39	20.2		28	25.2	11	13.4	
No	154	79.8		83	74.8	71	86.6	
Karnofsky PS			0.0001					0.094
<60	171	88.6		102	91.9	69	84.1	
>60	22	11.4		9	8.1	13	15.9	
B symptoms			0.428					0.437
No	91	47.2		56	50.5	46	56.1	
Yes	55	49.5		55	49.5	36	43.9	
REAL			0.0001					0.036
Indolent	104	53.9		51	45.9	53	64.7	
Aggressive	80	41.5		54	48.1	26	31.7	
Very aggressive	9	4.7		6	6	3	3.6	
Comorbidity			0.428					0.0001
Yes	102	52		42	37.8	60	73.2	
No	91	47.2		69	62.2	22	26.8	
Outcome			0.026					0.0001
Alive	81	41		61	54	20	24	
Dead	112	59		50	45	62	76	
Cause of death			0.001					0.150
Complications of therapy	7	6.3		2	4	5	8.1	
Disease progression	87	77.7		43	86	44	71	
Comorbidity	18	16.1		5	10	13	21	
Treatment toxicity			0.001					0.002
Yes	31	6.1		11	9.9	20	24.4	
No	162	83.9		100	90.1	62	75.6	

IPI: international prognostic index

Table 2. Treatment modality in patients with NHL

Treatment modality	Total 193		Age (years)			
	N	%	<65		≥65	
			N	%	N	%
Without treatment	19	9.84	7	3.63	12	6.22
With treatment	174	90.15	104	53.88	70	36.27
Surgery	9	5.12	6	3.45	3	1.72
Radiotherapy	1	0.57	1	0.57	0	0
Immuno (chemotherapy)	164	94.25	97	55.75	67	38.50
Anthracycline-based	135	77.58	90	51.72	45	25.86
Without anthracycline	29	16.67	6	3.45	23	13.22

groups was DLBCL; 49 (44.1%) patients < 65 years and 27 (32.9%) ≥65 years had this histologic type of NHL.

Response to treatment

Overall 174 (90.2%) patients were treated with the following modalities: (immuno)chemotherapy, radiotherapy or surgery, whilst 19 (9.8%) patients were treated only with supportive measures (Table 2). These 19 patients (7 younger and 12 elderly) had end-stage disease when first diagnosed, with Karnofsky PS <60, and /or ≥2 comorbidities and died shortly after admission. Twenty-nine (16.67%) patients were treated without anthracyclines, of whom 23 were elderly patients with indolent lymphoma or significant cardiovascular problems.

Seventy out of 174 (40.23%) treated patients achieved CR. Each treatment modality resulted in significantly lower CR rate in the elderly in comparison to younger NHL patients (28.6 vs. 71.4%; $p < 0.001$). Response to therapy for all patients tested by χ^2 test showed that there was significant difference in the chance of achieving CR regarding the following clinical factors: younger age ($p = 0.001$), IPI 0 or 1 ($p = 0.042$), good Karnofsky PS ($p = 0.023$), absence of complications after treatment ($p = 0.007$) and absence of comorbidities ($p < 0.001$). Univariate analysis in patients ≥65 years showed that the only statistically significant factor for achieving CR was disease stage ($p = 0.004$). In contrast, univariate analysis in patients <65 years showed that parameters for achieving CR were gender, stage of disease, presence of B symptoms, IPI and Karnofsky PS. Multivariate analysis indicated that gender and disease stage were independent prognostic parameters ($p = 0.011$ and $p = 0.001$, respectively) for achieving CR in patients <65 years.

Overall survival

At the time of final analysis 112 patients had died. Among them 50 patients (44.6%) were < 65 years and 62

(55.4%) ≥65 years ($p < 0.001$). The causes of death were: PD, side effects of therapy or comorbid condition. PD was by far the most frequent cause of death (87 patients or 77.7%, $p < 0.001$). Among them 43 (86%) patients were < 65 years and 44 (71%) ≥ 65 years ($p = 0.785$). A total of 18 (16%) patients died due to comorbid conditions: 5 patients (10%) <65 years and 13 (21%) ≥ 65 years ($p < 0.001$). Side effects of therapy were the cause of death in 7 (6.3%) patients: 2 patients (4%) <65 years and 5 (8.1%) ≥65 years ($p < 0.001$). However, there was no significant difference in the cause of death between younger and older patients ($p = 0.150$).

The relevance of the individual parameters of death for all patients tested by χ^2 test showed that numerous factors were significant: clinical stage ($p = 0.006$), lymphoma aggressiveness ($p = 0.041$) and type ($p = 0.032$), IPI ($p = 0.001$), LDH level ($p = 0.015$), presence of bulky disease ($p = 0.031$), Karnofsky PS ($p = 0.001$), presence of B symptoms ($p = 0.012$), presence of comorbidity ($p = 0.001$), and lower dose density ($p = 0.022$). Comparing younger and elderly patients, statistically significant parameters for death were: male gender ($p = 0.042$; Figure 1), clinical stage IV ($p = 0.015$; Figure 2), indolent type of lymphoma ($p = 0.045$; Figure 3), IPI 3 or 4 ($p < 0.0001$; Figure 4), presence of comorbidity ($p < 0.0001$; Figure 5) and toxic effects of therapy ($p = 0.045$; Figure 6).

Median follow up was 31.5 months (range 1-144). For patients <65 years, median follow up was 36.8 months (range 1-114) and for patients ≥65 years 24.8 months (range 1-98). Median OS for patients <65 years with indolent lymphoma was 36 months (range 24-114), with aggressive lymphoma 22 months (range 12-46), and with very aggressive lymphoma 14 months (range 1-27). Median survival time for patients ≥65 years diagnosed with indolent lymphoma was 17 months (range 10-98), with aggressive lymphoma 20 months (range 9-32), and with very aggressive lymphoma 1 month (range 1-6).

Multivariate analysis in patients <65 years showed that factors for shorter survival were: extranodal local-

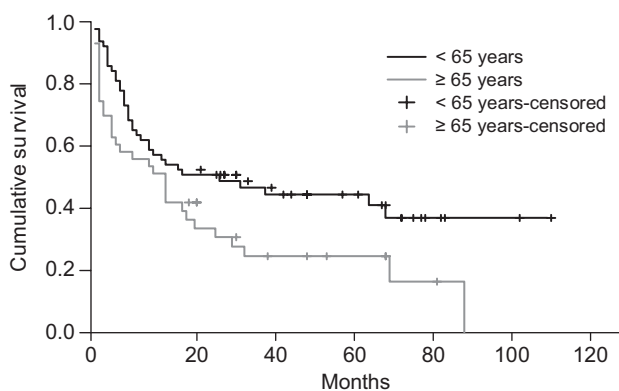


Figure 1. Kaplan-Meier overall survival in males (log rank test, $p < 0.042$).

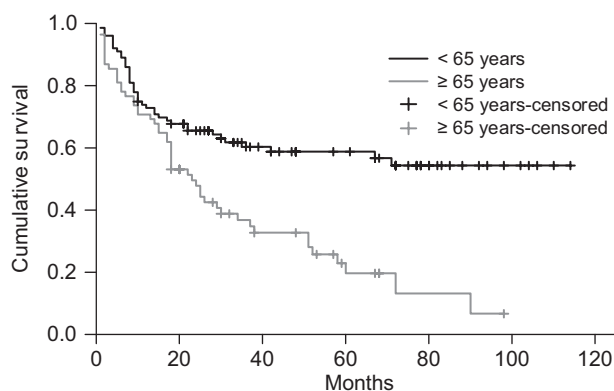


Figure 4. Kaplan-Meier overall survival in relation to IPI 3 and 4 (log rank test, $p < 0.0001$).

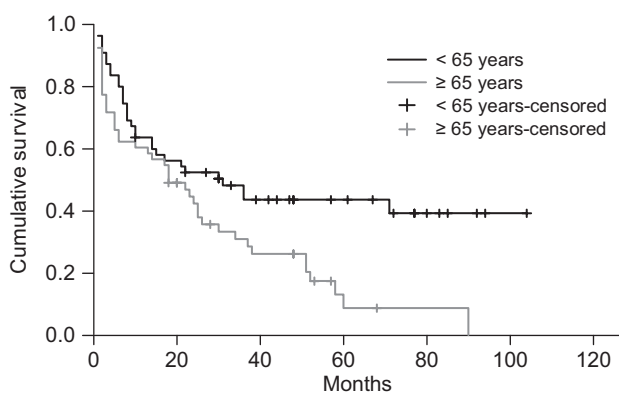


Figure 2. Kaplan-Meier overall survival in relation to clinical stage IV (log rank test, $p = 0.015$).

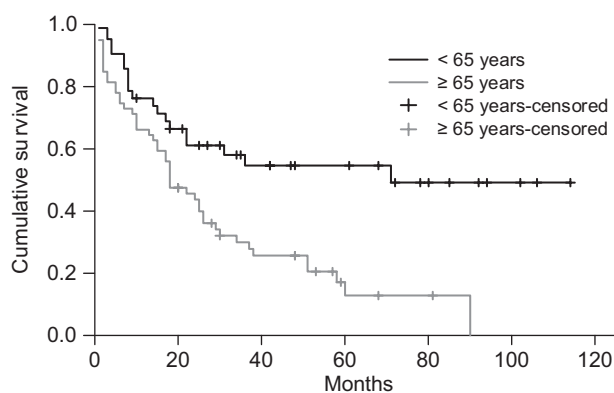


Figure 5. Kaplan-Meier overall survival regarding presence of comorbidity (log rank test, $p < 0.0001$).

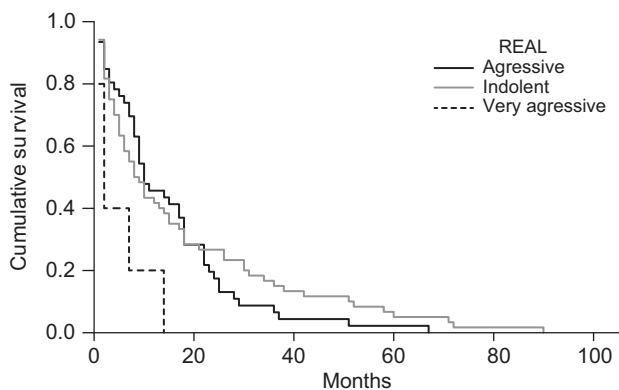


Figure 3. Kaplan-Meier overall survival regarding indolent lymphoma (log rank test, $p < 0.045$).

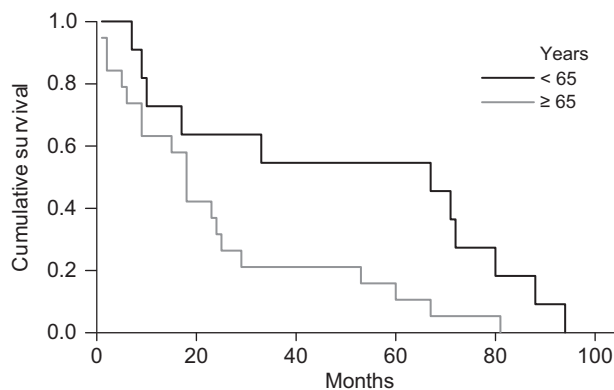


Figure 6. Kaplan-Meier overall survival regarding therapy toxicity (log rank test, $p = 0.045$).

ization, more aggressive lymphoma and high histological grade, high IPI, Karnofsky PS < 60 , and increased serum LDH. Multivariate analysis in patients ≥ 65 years showed that factors for shorter survival were Karnofsky PS < 60 , increased serum LDH and treatment toxicity (Table 3).

Discussion

The elderly represent a heterogeneous population, not categorized easily by chronological age alone. The definition of “elderly” may be variable, with age cut-offs of 60, 65 or 70 years in different studies and clinical

Table 3. Multivariate analysis of overall survival for patients ≥ 65 years

<i>Prognostic factors</i>	<i>SE</i>	<i>95% confidence interval</i>	<i>p-value</i>
Localization	0.324	0.810	0.190
Nodal			
Extranodal			
REAL	0.958	0.413	0.300
Indolent			
Aggressive			
Very aggressive			
Clinical stage	0.250	0.461	0.252
I, II			
III, IV			
B symptoms	0.329	0.575	0.782
Absent			
Present			
Histologic grade	0.842	0.166	0.865
Low			
Medium			
High			
Bulky disease	0.478	0.519	0.556
Yes			
No			
Karnofsky PS	0.429	1.486	0.004
<60			
>60			
IPI	0.252	0.810	0.261
0,1			
3,4			
LDH	0.353	0.218	0.019
Increased			
Normal			
Comorbidity	0.349	0.493	0.943
Yes			
No			
Treatment toxicity	0.601	0.910	0.040
Yes			
No			
Lower dose density	0.666	0.080	0.068
Yes			
No			

IPI: international prognostic index

trials. Lymphoma is a frequent disease in older patients and half of lymphoma cases occur in patients older than 65 years [4]. Moreover, the incidence of lymphoma in older patients has increased in recent years, probably more compared with younger patients, because older people is being increasing [4]. In our study, the annual incidence of NHL showed upward trend in both age groups during the follow up period. Some differences have been described regarding morphology and clinical presentation between younger and elderly patients with lymphoma. Also, the outcome in elderly patients with lymphoma is worse than in younger patients. Because of the poorer outcome of the elderly with NHL, the question arises as to whether NHL is intrinsically different in younger than in older patients.

Controversial findings about the prevalence of certain NHL subtypes among younger and older patients have been reported [7,14,15]. Overall, the most common is DLBCL [16-18], as in our study. One of the largest studies (conducted in 1997 among 8 referral centers) showed that elderly patients are more commonly diagnosed with small lymphocytic lymphoma (SLL), DLBCL, peripheral T lymphoma, and very rarely with anaplastic large cell, Burkitt and lymphoblastic lymphoma [4]. From a large population registry in the Netherlands it is also known that DLBCL is significantly more frequent among elderly patients, in contrast to follicular lymphoma [19]. The results of our study showed significant differences regarding the WHO histological grade. Intermediate grade NHL was more frequent in the younger patient group, and low grade NHL in the elderly patient group. This distribution could be explained by the more frequent diagnosis of follicular center cell (FCC) lymphoma and SLL in the elderly, and DLBCL in the younger patients. Compared to younger patients, elderly people have twice as much chance to be diagnosed with SLL and FCC.

In this study most of the cases had nodal localization without statistically significant difference between age groups. Among elderly patients, 42.7% had extranodal disease at presentation with gastrointestinal tract and bone marrow being the sites most frequently involved. Similarly, D'Amore and co-authors found that extranodal presentation (stomach 21% and bone marrow 16% of all extranodal cases) was more frequent among elderly patients [5]. According to data of Carbonea et al. in a series of 118 patients over 70 years of age, 62 NHLs (52.6%) were extranodal at presentation, the gastrointestinal tract being the most frequent site involved (47.3%) [7]. Hoerni et al. found extranodal disease in 39% of NHLs patients over 80 years of age [20]. The fact that extranodal presentation is relatively frequent in elderly patients with NHLs should be always emphasized considering its prognostic implications.

There is no clear evidence that the biology of the disease differs by age. A few studies that compared younger and elderly patients' features did not show consistent and substantial differences in these two age groups [16,18]. In our study group, B-symptoms were more frequent in younger patients, which could be explained by the more frequent prevalence of aggressive lymphomas in this age group, and the fact that elderly patients are often immunocompromised due to changes in their immunological response [17]. More aggressive histology of NHLs can also explain more frequent presence of "bulky" disease in patients <65 years. There was no statistically significant difference between distribution of clinical stage in different age groups, but clinical

cal stage II at presentation was more frequent in younger patients and clinical stage IV in elderly patients. The high prevalence of disseminated disease in elderly patients was also shown in other studies [17,21,24].

Elderly patients may have poor PS and other comorbidities, including decreased cardiac and renal function, and usage of multiple medications [22]. The prevalence of serious comorbidities in NHLs patients aged 60-69 years or over 70 years was 43% and 61%, respectively, in the study of Van Spronsen and colleagues [23]. For patients of 60-69 years and 70 years of age cardiovascular disease (15 and 22%, respectively), hypertension (14 and 14%, respectively), chronic obstructive pulmonary disease (6 and 10%, respectively) and diabetes mellitus (8 and 10%, respectively) were the most prevalent comorbid conditions [22]. The presence of comorbidities was not related to disease stage or histologic grade, but was associated with decreased OS within the first 4 months after diagnosis of NHL for all age groups [23]. In addition, in the presence of co-morbidity, 10-15% lower dose density chemotherapy was administered to elderly patients with NHLs [23].

Clinical studies [17,18] in elderly cancer patients have shown the negative impact of comorbidities on treatment response and prognosis. The influence of comorbidities on NHL treatment is unclear, but elderly patients with comorbidities were less likely to receive chemotherapy [24]. Unfortunately, comorbidities often influence the choice of treatment modality in elderly patients. Spronsen et al. found comorbid conditions in 60% of 1551 unselected lymphoma patients studied between 1995-2001 in the area of the population-based Eindhoven Cancer Registry, the Netherlands, with cardiovascular morbidity being the most frequent [24]. Varoczy et al. showed that elderly patients more often die of complications due to comorbidities than due to lymphoma progression [17]. On the contrary, in some studies comorbidity did not influence treatment response or survival [18,25].

In our study, patients ≥ 65 years had significantly more comorbid conditions in comparison with younger NHL patients (73.2 vs. 37.8%, $p < 0.0001$). Also, elderly NHL patients with comorbid condition(s) had statistically significant poorer treatment outcome, lower CR rates and higher death rates. Although treatment toxicity was not more frequently recorded in patients with comorbid condition(s), it is worth knowing that these patients have 70% greater chance of developing treatment toxicity.

The outcome of NHL patients is highly variable, and the histology of lymphoma is one of the major determinants of treatment outcome and prognosis. Age has been shown to be the most important prognostic factor, independently associated with poor survival in pa-

tients with intermediate and high grade NHL. Treatment approach to aggressive NHLs in the elderly is clearly defined. If comorbid conditions are not present, age should not influence treatment choice [21]. Treatment strategies in other NHL histologies are controversial, especially in the field of indolent lymphomas.

In our study, 174 out of 193 (90.2%) patients were treated with some treatment modality. Overall, 19 (9.8%) patients were treated with supportive measures only because they were at the end-stage of disease, with Karnofsky PS < 60 or with comorbidity, and died shortly after hospital admission. Chemotherapy, as the most frequent treatment modality, was equally represented in both age groups. However, in patients ≥ 65 years of age anthracycline protocols were significantly less used, may be due to higher prevalence of indolent lymphoma cases in the elderly and the presence of cardiovascular morbidity.

According to previous studies, CR rates decreased with age, from 68% in young patients to 45% in elderly patients [5,25,27], which was also registered in our study. In addition, disseminated disease (i.e. advanced clinical stage) was the most important prognostic factor for achieving CR in both of our patient age groups.

In a large Danish study, the following features were identified as poor prognostic indicators in elderly patients: hepatic involvement, presence of B-symptoms, high grade histology and elevated LDH [5]. In our study, Cox regression analysis also identified some pretreatment clinical features that were independent predictors for shorter survival: Karnofsky PS < 60 and increased serum LDH in both age groups. Additional parameters in the younger group were extranodal localization, more aggressive lymphoma, high histological grade and high IPI, whilst treatment toxicity significantly reduced survival in the elderly patients.

Conclusion

The most common cause of death in patients > 65 years is PD. Treatment decision in NHLs of the elderly should not be based only on patients age, but also on the presence of comorbid conditions and the risk of treatment toxicity. Therefore, elderly patients with NHLs should be treated with standard protocols (without dose reduction) in addition to adequate supportive measures.

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