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Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone is beneficial but toxic in very elderly patients with diffuse large B-cell lymphoma: a population-based cohort study on treatment, toxicity and outcome

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Abstract

To assess treatment strategies, toxicity and outcome in very elderly patients (aged ≥ 75 years) diagnosed with diffuse large B-cell lymphoma (DLBCL) in the rituximab era, an observational population-based cohort study was performed. From 103 patients with a median age of 81 years, data of clinical characteristics, treatment, toxicity and outcome were evaluated. Advanced stage DLBCL was documented in 74 patients. In 80 patients chemotherapy was initiated; 70 patients received rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). In this group, 39 patients completed all cycles and 30 patients achieved a complete remission. Severe chemotherapy-related toxicity occurred in 69%. Two-year overall survival was 70% for elderly patients who completed chemotherapy, 28% for those treated with incomplete or suboptimal chemotherapy and 21% for those receiving palliative radiotherapy or supportive care. In conclusion, the ability to complete R-CHOP was associated with better overall survival compared to other treatment strategies at the expense of severe treatment-related toxicity.

Keywords: Elderly, DLBCL, population-based, HemoBase

Introduction

Non-Hodgkin lymphoma is the most common lymphoid malignancy, with an incidence that increases exponentially with age. Since the life expectancy of the population is growing, clinicians are increasingly confronted with the clinical care of geriatric patients diagnosed with aggressive lymphoma such as diffuse large B-cell lymphoma (DLBCL) [1,2]. The addition of rituximab to cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in DLBCL improved the survival dramatically in both young and elderly patients [3,4]. Although small pre-selected populations of patients aged 75–80 years were included in these studies [3,5], due to age, comorbidity and functional status these patients are often excluded from the trials. Detailed information on treatment decision, offered treatment protocols, toxicity and long-term outcome in unselected very elderly patients with DLBCL is minimal, and was predominantly gathered in the pre-rituximab era [6]. Thus, trial outcomes in healthier and younger adults may not be applicable to the elderly, who represent the majority of patients receiving treatment.

To our knowledge, detailed information from a population-based registry, with emphasis on survival benefit of rituximab in R-CHOP therapy in the very elderly, has not yet been published. To reflect actual practice and to investigate whether very elderly patients with DLBCL are offered R-CHOP chemotherapy, we performed this observational, population-based, cohort study of all patients older than 75 years, diagnosed with DLBCL.

Methods

Background

Starting in 2005, all patients from the five medical centers in Friesland, a province in the northern part of The Netherlands

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with 650 000 inhabitants, diagnosed with a hematological malignancy were prospectively registered in HemoBase for objective assessment of clinical parameters and for research purposes. HemoBase is a web-based, multidisciplinary, population-based electronic health record specifically designed by professionals in hemato-oncology. With direct registration by professionals involved in the diagnostic work-up and treatment, the database is representative of the incidence, characteristics and treatment of patients with a hematological malignancy in the entire Friesland area [7].

Study design and patient identification

This was an observational population-based cohort study examining treatment characteristics and outcomes for all patients older than 75 years, diagnosed with DLBCL, in Friesland during a 7-year period from 1 January 2005 through 31 December 2011. All relevant data of clinical characteristics, laboratory tests, treatment, treatment-related toxicity and outcome were retrieved from Hemo-Base and local patient records. The age-adjusted International Prognostic Index (aa-IPI) was calculated for each patient. Histological diagnoses were made on the first nodal or extranodal biopsy according to the World Health Organization (WHO) classification [8]. All histological diagnoses were reviewed by a panel of three experienced hematopathologists. In an instance of persistent discrepancy, cases were submitted to the national lymphoma panel for review. To ensure that all diagnoses of DLBCL were captured, the HemoBase dataset was compared with the National Cancer Registry, without any discrepancies. Clinical information was retrievable for more than 99% of patients identified by the initial search. Patients with recurrent DLBCL, primary cutaneous DLBCL or another type of aggressive lymphoma were excluded (Figure 1).

Treatment and toxicity

Modality of treatment was divided into four groups. The first group received either R-CHOP-14 or R-CHOP-21 chemotherapy with curative intent. In the second group, other, suboptimal, rituximab-containing chemotherapeutic regimens were given. The third group received only palliative radiotherapy and the fourth group supportive care. Dose reductions, defined as more than 20% reduction of cyclophosphamide or doxorubicin, were retrieved from HemoBase. The administration of granulocyte colony-stimulating factor (G-CSF) was registered. All treatment-related toxicity resulting in hospitalization was retrieved from the hospital files and classified according to common toxicity criteria (CTC) [9]. These complications were further categorized into the following subgroups: neutropenic fever and infections, cardiotoxicity, pulmonary toxicity, gastrointestinal side effects and a remaining group with other complications.

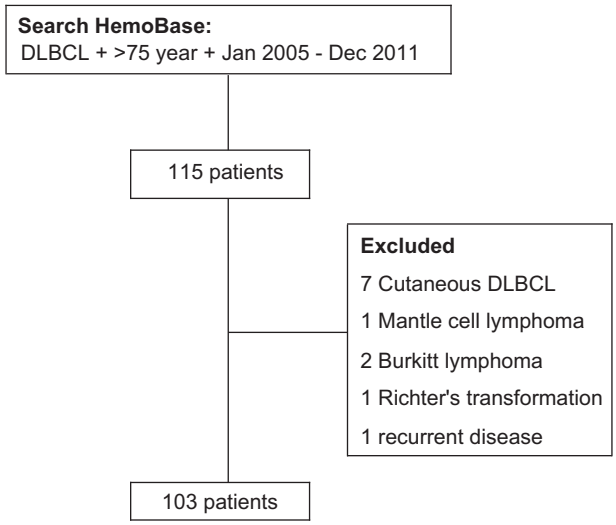

Figure 1. Search in HemoBase. After exclusion of recurrent DLBCL, primary cutaneous DLBCL or other type of aggressive lymphoma, 103 patients were eligible for the study.

Follow-up

Follow-up was completed until 31 January 2012. Tumor responses in patients who completed R-CHOP therapy were classified as complete remission (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the International Working Group [10]. Recurrent or progressive disease was documented. General practitioners were contacted about the current status of those patients for whom outcome was not recorded in HemoBase. In the case of death, causality with disease or received treatment was noted. Approval was obtained from the Medical Ethics Review Committee of the Medical Center Leeuwarden for this observational study. Informed consent was waived, in accordance with Dutch regulations.

Statistical analysis

The primary end point was overall survival (OS), defined as the time from diagnosis until death or last follow-up. Survival curves were estimated according to the Kaplan–Meier method. Between-group differences in OS were evaluated using the log-rank test. In this, survival of patients who completed chemotherapy and those who received suboptimal chemotherapy or alternative treatment regimens was compared.

All categorical variables are expressed as counts and percentages. Where applicable, differences between groups were evaluated by Fisher's exact (for binary variables) or χ^2 tests. A two-tailed p-value of less than 0.05 indicated statistical significance.

All analyses were performed using commercially available computer software (Statistical Analysis System version 9.2; SAS Institute, Cary, NC).

Results

Clinical characteristics

From January 2005 until December 2011, 115 patients of 75 years and older were diagnosed with DLBCL, of whom 103 patients were eligible for the study (Figure 1). The median age was 81 years (range 75–96 years) with slightly more female patients (57%); 57% of the patients had a good performance status (WHO 0–1). Advanced disease (Ann Arbor stage 2–4) was seen in 71% of the cases. In 10 patients

staging was not performed. An advanced aa-IPI (score 2–3) was documented in 36 patients, while in 19 patients the aa-IPI was not assessed (Table I).

Treatment and adaptations in therapy

The majority of patients (78%) received chemotherapy; all chemotherapeutic regimens were rituximab-based. In 70 patients R-CHOP therapy was initiated with curative intent, with 13 patients treated for stage 1 disease. Seven patients were treated with R-CHOP-14; the remainder received R-CHOP-21. Another 10 patients received other, suboptimal, chemotherapy. In nine patients radiotherapy was given as the only treatment, and 12 patients received supportive care. In two patients the treatment modality was unknown (Table II).

The planned R-CHOP schedule was completed by 39 patients: 23 patients received six cycles, eight patients eight cycles and eight patients with stage 1 disease three cycles with radiotherapy. The alternative chemotherapeutic regimens included R-LL(O)P (rituximab, chlorambucil, vincristine, procarbazine, prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone). Three patients in this group received six or more cycles. In the 70 patients treated with R-CHOP, 22 (31%) received a dose reduction at the start of treatment, without clear argumentation in the majority of patients (68%). Of this group only three patients received full-dose chemotherapy afterward. Another six patients received dose reduction during treatment, all because of toxicity. Dose reduction did not increase the likelihood of completing R-CHOP. G-CSF was offered to 25 patients (31%) receiving chemotherapy, predominantly because of the R-CHOP-14 schedule or the occurrence of neutropenic fever.

Table I. Patient demographics and clinical characteristics.

Clinical characteristics	*n*	Percentage
Total group	103	
Sex		
Male	44	43
Female	59	57
Age		
75–80	46	45
81–85	35	34
86–90	17	16
>90	5	5
WHO performance status		
0	22	21
1	37	36
2	16	16
3	12	11
Unknown	16	16
Ann Arbor staging		
1	19	19
2	23	22
3	20	19
4	31	30
Unknown	10	10
A	71	68
B	16	16
Unknown	16	16
LDH*		
N	53	51
1–1.5	25	24
>1.5	18	18
Unknown	7	7
Extranodal disease		
0	46	45
1	27	26
>1	22	21
Unknown	8	8
Age-adjusted IPI		
0	24	23
1	24	23
2	23	22
3	13	13
Unknown	19	19

WHO, World Health Organization; LDH, lactate dehydrogenase; IPI, International Prognostic Index.
*Classified as N (normal value) or 1–1.5 or more then 1.5 times above the normal value.

Table II. Treatment, adaptations and treatment-related toxicity.

	n	Percentage
Treatment		
Chemotherapy	80	78
R-CHOP	70	68
R-CHOP-14	7	
Unknown scheme	10	10
Radiotherapy only	9	9
Supportive care	12	11
Other	2	2
Dose reduction R-CHOP		
First cycle	22	31
Arguments		
Age	6	27
Cytopenia	1	5
Unknown	15	68
Full dose after first dose	3	
During treatment	6	9
Arguments		
Toxicity	6	
Number of cycles		
In R-CHOP chemotherapy	70	
Complete (6 or 8 or 3 + RT*)	39	56
1	13	17
2–5	18	27
In alternative chemotherapy	10	
1	2	
2–5	5	
6 or more	3	
Arguments incomplete chemotherapy	38	48
Complication treatment	12	15
Death	9	
Patient's decision	7	9
Progressive disease	7	9
Death	2	
Performance status decline	5	6
Death other cause	3	4
Death unknown cause	1	1
Other	3	4
G-CSF		
Yes	25	31
No	32	40
Unknown/not documented	23	29
Patients with one or more complications	55	69
Number of complications	88	
Febrile neutropenia/infections	57	65
Febrile neutropenia	37	
Proven infections	20	
Sepsis/septic shock	6	
Urinary tract infection	6	
Pneumonia	7	
Herpes zoster	1	
Cardiotoxicity	4	5
Gastrointestinal toxicity	13	14
Pulmonary disease	2	2
General malaise	4	5
Other	8	9

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone; RT, radiotherapy; G-CSF, granulocyte colony-stimulating factor.
*Eight patients 3 + RT.

Follow-up and survival

Thirty patients who completed the planned schedule achieved a CR at response evaluation. Another six patients achieved PR, one patient had PD and in two patients response evaluation was not performed. Recurrent or PD was documented in 18 patients (23%), of whom 13 completed all cycles of R-CHOP. Second-line treatment was given in 14 patients, with radiotherapy as the main modality. Median survival time was 11 months (1–79 months), with a median follow-up duration in surviving patients of 32 months. One year and 2-year OS were, respectively, 50% and 42% for the entire population (Figure 2). For all R-CHOP patients, 1- and 2-year OS were, respectively, 60% and 51%. Based on the different treatment regimens patients were categorized into three groups. The first group completed all R-CHOP cycles, in the second group suboptimal (incomplete R-CHOP and other chemotherapeutic regimens) therapy was given, and the third group received palliative radiotherapy or supportive care. At baseline, the patients treated with palliative therapy were significantly older and had a higher aa-IPI and WHO performance status in comparison with those receiving chemotherapy. In patients capable of completing R-CHOP, only WHO performance status was significantly better at baseline compared with patients treated with suboptimal chemotherapy. OS at 1 year for these subgroups was 87%, 31% and 21%, respectively, and at 2 years 70%, 28% and 21% (Figure 3). Completing chemotherapy was significantly associated with a better survival ($p < 0.001$). Completing R-CHOP with initial dose reduction or during treatment did not significantly alter the outcome (Figure 4). Furthermore, OS remained superior compared with patients with incomplete R-CHOP in whom treatment was electively ended by either patient or physician (Figure 5). In Table III the deaths during follow-up are depicted.

Treatment-related toxicity

In 31 patients (39%), incomplete rituximab-containing chemotherapy was given, with 13 patients receiving only one cycle, mainly because of treatment-related toxicity (Table I). Other reasons to end treatment included patient's own decision (9%), decline in performance status (6%), progressive disease (9%) and death from another cause (5%). Ten toxicity-related deaths occurred during R-CHOP treatment. Sepsis was the major cause of death and the first complication in eight patients. Two-thirds of the patients treated with chemotherapy experienced toxicity, predominantly febrile neutropenia and infections, mainly of bacterial origin (Table II). Other complications are listed in Table II. In 15 of the 55 patients (27%) a complication developed, although initial dose reduction was given. Increasing age was not related to either the occurrence of complications or the rate of incomplete chemotherapy (data not shown).

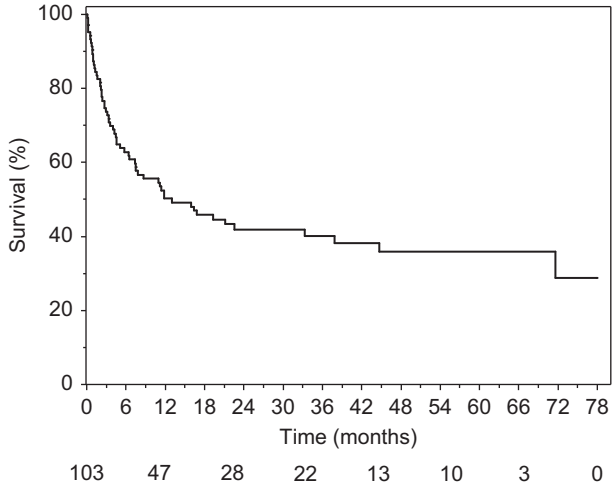

Figure 2. Overall survival of 103 elderly patients with DLBCL.

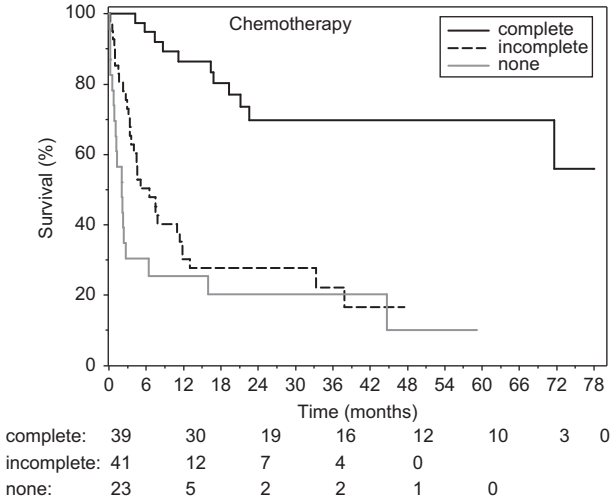

Figure 3. Overall survival for three subgroups: the first group completed all cycles of R-CHOP, the second group received suboptimal therapy (incomplete R-CHOP or other chemotherapeutic regimens) and in the third group only palliative radiotherapy or supportive care was given. Two-year OS was 70%, 28% and 21%, respectively.

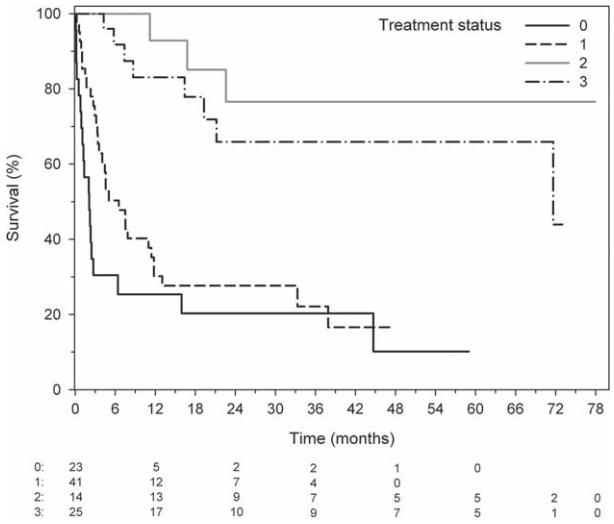

Figure 4. Overall survival for four subgroups, defined as 0: no chemotherapy; 1: incomplete chemotherapy; 2: complete R-CHOP with dose reduction; 3: complete R-CHOP without dose reduction. Outcome of patients completing R-CHOP with and without dose reduction is not significantly different ($p = 0.39$).

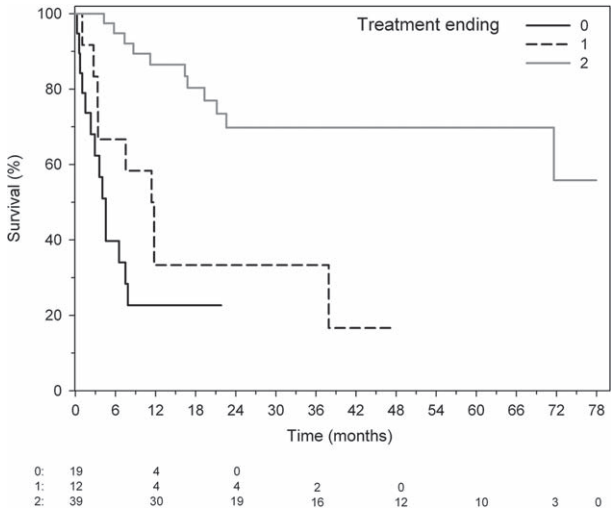

Figure 5. Overall survival divided into three subgroups: 0: patients with incomplete R-CHOP, not electively ended; 1: patients with incomplete R-CHOP, electively ended; 2: patients who completed R-CHOP. Outcome of the two subgroups in incomplete R-CHOP is not significantly different ($p = 0.19$) and OS in complete R-CHOP remained superior.

Incomplete assessments

In our cohort, the standard clinical assessment, laboratory tests and computed tomography (CT) scans were not fully performed in 19 patients. The majority (62%) of these patients did not receive treatment with curative intent. The survival analysis of this specific group showed that 16 patients had died with a median survival of only 2.2 months (range 0–48) (data not shown). Hence, we considered the incomplete assessments a reflection of the poor performance status and inability to undergo clinical procedures. In the R-CHOP group, in only six of the 70 patients was the standard clinical assessment not fully performed.

Discussion

In this population-based cohort study we followed all patients, older than 75 years, with newly diagnosed DLBCL during a 7-year period in a well-defined geographic area. In this, our data reflect common clinical practice in the elderly with DLBCL in the rituximab era. The majority of these patients received R-CHOP chemotherapy with curative intent. Our rate for initiating chemotherapy in these elderly patients compares favorably with previous reports from the pre-rituximab era. These earlier studies showed that in only 4–46% of the very elderly with DLBCL was anthracycline-based chemotherapy applied [1,2,6,11,12]. Reported superior outcome with monoclonal antibodies, better supportive care and patient awareness of novel therapies might be considerations for hematologists to offer R-CHOP chemotherapy increasingly to the very elderly. This study demonstrates that 56% of the patients who started with R-CHOP chemotherapy could complete the standard regimen, of whom the majority (77%) achieved a CR. Our observed CR rates are 20% higher than CR rates reported in other population-based studies [6,11] and older phase III trials in the pre-rituximab era [13], illustrating the efficacy of rituximab in DLBCL treatment. Our 2-year OS of patients capable of completing intensive treatment is in line with a population-based retrospective analysis from British Columbia (70% vs. 73%) [14]. Comparing our data with population-based data for very elderly patients treated with CHOP [6], a potential benefit of rituximab was observed. In the latter study, a progressive decline in survival was seen, with a 5-year survival of 38% in patients who received complete CHOP therapy, whereas our survival curves clearly showed a plateau phase, with a 5-year survival of more then 50%. In conclusion, very elderly fit patients who can complete standard R-CHOP therapy also benefit from intensive treatment and rituximab like their younger counterparts, and these outcomes show that age is not an absolute criterion for withholding intensive treatment.

The drawback of intensive chemotherapy in this elderly population is reflected by a high rate of treatment-related toxicity. The majority (69%) of patients experienced at least one complication for which hospitalization was required. Most common observed toxicities were infections and neutropenic fever. In patients treated with R-CHOP, eight of the 10 toxic deaths were attributed to therapy-refractory sepsis. Our rates of death from toxicity (14%) are comparable to those reported in retrospective studies and trials in this population (range 7–20%) [5,6,12,13,15]. Although high percentages of severe toxicity have been previously reported in the very elderly treated with CHOP [6,13], the proportion of proven infections (23%) and neutropenic fever (42%) in this cohort is remarkable. Elderly persons are more prone to develop complications, due to alterations in pharmacokinetics with change of lean body mass and hepatic and renal function. Moreover, decreased stem cell reserve can complicate treatment. Measures to reduce infectious threats in these elderly patients include initiating prophylactic G-CSF, antibiotics or pretreatment with corticosteroids [16]. A third of our population received G-CSF after the occurrence of neutropenic fever; prophylactic use was only applied in patients treated with R-CHOP-14 ($n = 7$). The guidelines of

Table III. Reasons for death according to treatment received.

			Main reason for death			
Treatment	Total number	Death	Disease	Toxicity	Other cause	Unknown
R-CHOP[1]	70	34	14	10	6	4
Other regime	10	8	3	0	2	3
Radiotherapy	9	5	3	0	1	1
Supportive	12	12	11	0	1	0
Unknown	2	2	0	0	0	2
Total	103	61	31	10	10	10

[1]R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone.

the European Organisation for Research and Treatment of Cancer (EORTC) and the American Society of Clinical Oncology (ASCO) recommend prophylactic use of G-CSF when the risk of developing neutropenic fever is more than 20% [17,18]. Elderly patients treated with (R-)CHOP are defined as high risk, in whom incidence rates of 27–47% are reported as well as an increased mortality [18]. The prophylactic use of G-CSF significantly reduces the risk of neutropenic fever and infections, while the effects on overall survival are less clear [19–21]. The higher incidence of neutropenic infections in this cohort might be attributable to the underuse of G-CSF. The use of antibiotic prophylaxis may also reduce the incidence of febrile neutropenia, infections and hospitalization [22–24]; however, this approach raises concerns about the development of antimicrobial resistance [25].

High grade toxicity was the main reason for cessation of therapy, and occurred in 15% of patients treated with rituximab-based chemotherapy. The survival and outcome of patients exposed to fewer cycles of chemotherapy was only slightly better than for those who received radiotherapy or other palliative treatment (2-year survival, respectively, 28% and 21%). This underscores the importance of accurate patient selection. Dose reduction, undergone by 40% of patients treated with R-CHOP chemotherapy, did not increase the likelihood of completing treatment. Accurate dose reduction rates in the elderly with DLBCL could be generated, due to the prospective registration of the administered chemotherapy by the clinician in our database. Our observed percentages of adaptations of treatment from actual practice are higher than those reported in trials and retrospective studies [6,26]. Dose adaptation was performed at the discretion and from the clinical viewpoint of the treating physician, and arguments were not often documented.

With R-CHOP given in the majority of patients, our proportion of patients receiving anthracyclines was significantly higher than that shown in a recent population-based analysis using the Surveillance, Epidemiology and End Results (SEER)–Medicare database [27]. This study elegantly showed the benefit of rituximab in chemotherapy in elderly patients, also without the use of anthracyclines. In order to address toxicity in the frail elderly, many other treatment strategies has been proposed. Attenuated chemotherapy, named R-miniCHOP, has shown good efficacy and safety in patients with DLBCL older than 80 years [15]. Although the CR and 2-year OS rates in that phase II trial were lower than in our population-based study with full dose therapy, the toxicity profile of R-miniCHOP was superior [15]. Other immunochemotherapy schedules without doxorubicin followed by rituximab maintenance or dose-adjusted infusional CHOP (DA-POCH-R) have also been shown to be a reasonable alternative for poor-prognosis DLBCL [28,29]. A recent retrospective study showed promising results of the use of rituximab–bendamustine in frail and comorbid elderly patients who were not eligible for standard chemotherapy [30], which will be further assessed in a prospective phase II trial. As illustrated in our study, the majority of severe toxicity, including toxicity-related deaths, occurred during the first cycle of therapy. This "first cycle effect" might be overcome with pre-phase treatment to improve the tolerance to chemotherapy before administration of a full-dose cycle [24].

Detailed information of the performance status and stage was not documented in 18% of patients. This appeared to be a specific subgroup with a pre-existing poor performance status or high grade comorbidity, reflected by a very poor prognosis, with palliative treatment as major chosen modality. Geriatric assessment was only sporadically performed and described. The assessment of whether a patient was fit enough for chemotherapy appeared to be dependent on the judgement of the clinician. In deciding the optimal treatment for elderly patients, the usefulness of a comprehensive geriatric assessment (CGA) in identifying the frail elderly has been shown in several studies [31–34]. However, as illustrated in our population-based study, CGA is time-consuming and seldom implemented in daily clinical practice. Other more practical risk scores to asses functional status includes the Charlson Comorbidity Index (CCI) [35,36], Activities of Daily Living (ADL) [15], the Vulnerable Elderly Survey [37] and the Groningen Frailty Indicator (GFI) [38]. Since the GFI appeared to be an independent prognostic factor in survival in elderly patients with hematological malignancies, it might be a useful screening tool to discriminate frail from fit elderly with DLBCL and identify those who may benefit from intensive chemotherapy [32].

This study illustrates the strength of investigator- and physician-initiated population-based registries. Underrepresentation of older adults in cancer registration trials and poor enrollment among elderly patients in phase III studies is a well-defined problem [39]. Decline in functional reserve, increased comorbidity with concomitant medication use and insufficient social support are the main factors for not fulfilling the inclusion criteria. Hence, frequently, the age of trial populations differs substantially from that of the general population, and the conclusions from these trials may not be applicable to patients in daily practice. Furthermore, adverse effect profiles in relation to OS can remain poorly characterized. Population-based registries, such as HemoBase in our study, can play an important role in closing the gap between patients in phase III trials and the general patient population. As shown in this study, it offers pools of prospectively gathered data to study long-term efficacy and toxicity in at-risk patients with lymphoma. Data from population-based registries, especially in older adults with cancer, can guide treatment decisions and future directives in trial design. Novel trial designs tailored to the elderly may result in better trial participation by both patients and physicians.

In conclusion, over a period of 7 years, the majority of patients in Friesland with DLBCL and aged ≥ 75 years were treated with a R-CHOP regimen and were able to complete this treatment. The ability to complete such an intensive treatment was significantly associated with a better 2-year survival compared to suboptimal chemotherapy, or palliative supportive care. Severe treatment-related toxicity was observed in two-thirds of patients, and might be due to underuse of prophylactic G-CSF. Age alone is a poor indicator to differentiate the fit elderly patient, who will benefit from intensive therapy, from the frail patient. Other strategies for patient selection, such as the implication of a comprehensive

geriatric assessment, should be further evaluated in very elderly patients with DLBCL.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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