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ORIGINAL ARTICLE

Health-related quality of life and persistent symptoms in relation to (R-)CHOP14, (R-)CHOP21, and other therapies among patients with diffuse large B-cell lymphoma: results of the population-based PHAROS-registry

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Abstract The increasing number of longer-living patients with diffuse large B-cell lymphoma (DLBCL) and serious side effects of treatment urged us to study the health-related quality of life (HRQoL) and persistent (treatment-related) symptoms in unselected patients after different treatment modalities and compare HRQoL of patients with a normative population. The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with DLBCL from 2004 to 2010. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was completed twice, with a 1-year interval. Detailed data on treatment were extracted from the Population-based HAematological Registry for Observational Studies. Two hundred fifty-six patients responded (84 %, T1). Compared to patients treated with rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone every 21 days ((R-)CHOP21), those who underwent (R-)CHOP14 more often reported tingling in the hands and feet (27 vs 42 %, $p=0.02$) and fatigue (35 vs 46 %, $p=0.03$) and reported a lower global health status/HRQoL. Mean HRQoL was statistically and clinically relevantly lower among DLBCL patients compared to a normative population ($p<0.01$). Persistent tingling in hands/feet was reported more often by older patients and patients treated with (R-)CHOP14 independently of the other characteristics. Furthermore, patients who reported symptoms exhibited significantly lower HRQoL compared to patients without symptoms/worries. Patients treated with (R-)CHOP14 reported more neuropathic symptoms, more fatigue, and a lower HRQoL than patients treated with (R-)CHOP21. Alertness for persistent symptoms that occur during and after treatment of DLBCL patients is needed and may help to avoid lasting negative influence on their HRQoL.

Keywords Quality of life · Non-Hodgkin lymphoma · Diffuse large B-cell lymphoma · Cancer survivors · Population-based · Treatment · PHAROS · PROFILES

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Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies and is the most common hematologic malignant neoplasm in adults. In the United States, there were approximately 510,000 people alive who had a history of NHL on January 1, 2010 [1], and the 10-year prevalence of aggressive NHL in the Netherlands, with 6,570 patients in the year 2009, is expected to increase to approximately 10,600 patients in

2020 [2]. Diffuse large B-Cell lymphoma (DLBCL) is the most common subtype, accounting for approximately 30–40 % of NHL [3, 4].

Traditionally, treatment of DLBCL included the cyclophosphamide, doxorubicin, vincristine, and prednisone(CHOP) regimen [5]. With the addition of rituximab (R), response rates and overall survival have improved significantly, defining rituximab combined with CHOP ((R-)CHOP) as the new standard treatment for patients with DLBCL [3, 6, 7] whereby CHOP every 14 days seemed superior to a 21-day schedule, with respect to overall survival [8]. However, recently, two studies showed that overall survival in patients treated with (R-)CHOP14 was not superior to patients treated with (R-)CHOP21 [9, 10]. Patients with recurrent disease are treated with high-dose chemotherapy (HDCT) combined with autologous stem cell transplantation (ASCT).

The increasing number of DLBCL patients that are being treated with changing treatment regimens requires a careful evaluation not only of survival improvements but also regarding potential side effects of treatment and (long-term) health-related quality of life (HRQoL). HRQoL is a multidimensional construct that covers patients' perceptions of his or her physical, emotional, social, and cognitive functions and disease and/or treatment-related symptoms and represents patients' subjective experience with cancer.

Up to now, some studies have investigated HRQoL among aggressive lymphoma patients [11–13] and a few among DLBCL patients [14, 15]; however, most studies were randomized clinical trials or had a cross-sectional design. As a consequence, elderly patients and patients with comorbidities were underrepresented, or HRQoL was only assessed at one time point. Furthermore, a comparison of (long-term) HRQoL between patients treated with (R-)CHOP14 or (R-)CHOP21 has never been made.

The aims of the present study were therefore to (1) evaluate (long-term) HRQoL and symptoms/worries of DLBCL patients on two time points in a population-based setting that includes these previously underrepresented patients and compare them with an age-and sex-matched normative population, (2) compare HRQoL and symptoms/worries between patients treated with (R-)CHOP14 or (R-)CHOP21 up to 5-year posttreatment, and (3) assess the prevalence of persistent symptoms/worries and identify associated clinical and/or sociodemographic characteristics. We hypothesized that HRQoL would be deteriorated in patients compared to the normative population. We furthermore hypothesized that patients treated with (R-)CHOP14 would report a lower HRQoL and more symptoms than patients treated with (R-)CHOP21.

Methods

Setting and population

This study took place within the scope of the Population-based HAematological Registry for Observational Studies (PHAROS), an extension of the Netherlands Cancer Registry (NCR). The NCR was used to select all patients who were diagnosed with DLBCL as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3) [16] between January 1, 2004 and December 31, 2010 in an area covering approximately 40 % of the Dutch population. The NCR data of these patients (including date of diagnosis, morphology, gender, date of birth, and stage) were replenished with details on treatment, adverse events, and treatment outcomes from PHAROS.

Additionally, a longitudinal population-based survey was set up among DLBCL patients registered with the Eindhoven Cancer Registry (ECR) which fills about 15 % of NCR. The database with patients diagnosed between January 1, 2004 and December 31, 2010 was linked with the database of the Central Bureau for Genealogy to exclude patients who were deceased. HRQoL and symptoms were collected within patient reported outcomes following initial treatment and long-term evaluation of survivorship (PROFILES). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors [17].

Questionnaires were sent out in batches, and this was done on three time points. In May 2009, patients diagnosed between January 2004 and January 2009 were included in the study and received the first questionnaire. In November 2009 and May 2011, patients newly diagnosed after the last inclusion date were subsequently invited to participate (T1) to include all patients up to December 31, 2010. Patients received the subsequent questionnaire (T2) 1 year after T1. Ethical approval for the study was obtained from a certified medical ethics committee (of the Maxima Medical Centre in Veldhoven, The Netherlands; number 0734).

Study measures

The Dutch-validated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used to assess HRQoL [18]. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single-item measures range in score from 0 to 100. A higher score on function scales and global health and quality of life scale implies a better HRQoL, whereas for symptoms with a higher score refers to more symptoms [18].

The Dutch version of the EORTC CLL-16 was used to assess disease and treatment-related specific symptoms and worries. This questionnaire was originally developed for patients with chronic lymphocytic leukemia but is also applicable to lymphoma patients. The symptom tingling in hands/feet was added to this questionnaire, as it appeared from the literature and interactions with patients that this might be a prevalent symptom. Answer categories range from one (not at all) to four (very much).

Comorbidity at the time of survey was categorized according to the adapted self-administered comorbidity questionnaire (SCQ) [19]. Patients' marital status and educational level were also assessed in the questionnaire. Clinical data were obtained from the NCR and PHAROS.

If patients received more than one treatment line, the treatment category was based on the sum of treatments before completion of the questionnaire and was ordered from most to least expected impact on HRQoL: (1) ASCT, (2) HDCT, (3) (R-)CHOP14, (4) (R-)CHOP21, and (5) other chemotherapy (CT), radiotherapy (RT), or no therapy.

Normative population

The normative population was selected from a reference cohort of 2,040 individuals from the general Dutch population (CentER panel). The set of questionnaires completed by this normative population in November 2011 included the EORTC QLQ-C30, SCQ, and data on sociodemographics. This cohort is considered as representative for the Dutch-speaking population in the Netherlands [20]. Based upon this normative population, an age- and sex-matched selection was made of 425 persons to compare HRQoL with the DLBCL patients. For matching, ten strata were formed using sex and age (five categories). Within each stratum, a maximum number of persons from the reference cohort were randomly matched according to the "strata frequency distribution" of the patients. This resulted in 425 matched cancer-free panel members for 256 patients.

Statistical analyses

Differences in sociodemographic and clinical characteristics between respondents and nonrespondents or patients with unverifiable addresses, between patients who completed one or two questionnaires, and between patients treated with (R-)CHOP14 or (R-)CHOP21 were compared with chi-square or *t* tests where appropriate.

The mean QLQ-C30 scores from the DLBCL patients were compared with the mean scores of an age- and sex-matched Dutch normative population using independent sample *t* tests.

Analyses of covariance (ANCOVA) were carried out to compare the mean QLQ-C30 scores, and logistic regression analyses were used to compare the prevalence of CLL-16 symptoms and tingling in hands/feet between patients treated with (R-) CHOP14 or (R-)CHOP21 adjusted for age, number of comorbidities, time since treatment, and number of treatment cycles. Logistic regression analyses were also used to compare the prevalence of CLL-16 symptoms per time since treatment category stratified per treatment (i.e., (R-)CHOP14 or (R-)CHOP21), adjusted for age and number of comorbidities. Symptoms/worries were dichotomized as present (answer categories "a bit," "quite a bit," or "very much") or not present (answer category "not at all").

Multivariate logistic regression analyses were constructed to investigate the independent association between sociodemographic and clinical variables and the five most frequently reported persistent symptoms/worries and to assess the variance in the QLQ-C30 global health status/HRQoL scale explained by these symptoms/worries. Persistent symptoms/worries were defined by patients who had a specific symptom on both T1 and T2, and factors were a priori determined, including sex, age, number of comorbidities, time since diagnosis, stage, treatment, and number of treatment cycles. Since we observed multicollinearity between treatment and number of treatment cycles, we ran the analysis twice, once with treatment and once with number or treatment cycles.

ANCOVA were also carried out to compare the mean EORTC QLQ-C30 global health status/HRQoL scale between patients with or without persistent symptoms/worries adjusted for sex, age, number of comorbidities, and time since diagnosis. Persistent symptoms were defined as symptoms present at both T1 and T2.

All statistical analyses were performed using SAS (version 9.3 for Windows; SAS Institute Inc., Cary, NC). p values of <0.05 were considered statistically significant. Clinically relevant differences were determined using the evidence-based guidelines for interpretation of the EORTC QLQ-C30 between groups [21]. Patients were determined to be fatigued with a QLQ-C30 fatigue score >21.9 (mean of age- and sex-matched normative population + small clinically important difference, i.e., five points).

Results

Patients and normative population

Two hundred fifty-six DLBCL patients completed the first questionnaire (T1, 84 % response rate; Fig. 1), and subsequently, 130 patients completed the questionnaire again 1 year later (T2). The mean age at baseline survey completion was 63.5 years, and 66 % were male (Table 1). Mean time since diagnosis was 2.6 years, and 93 % of patients underwent one treatment line.

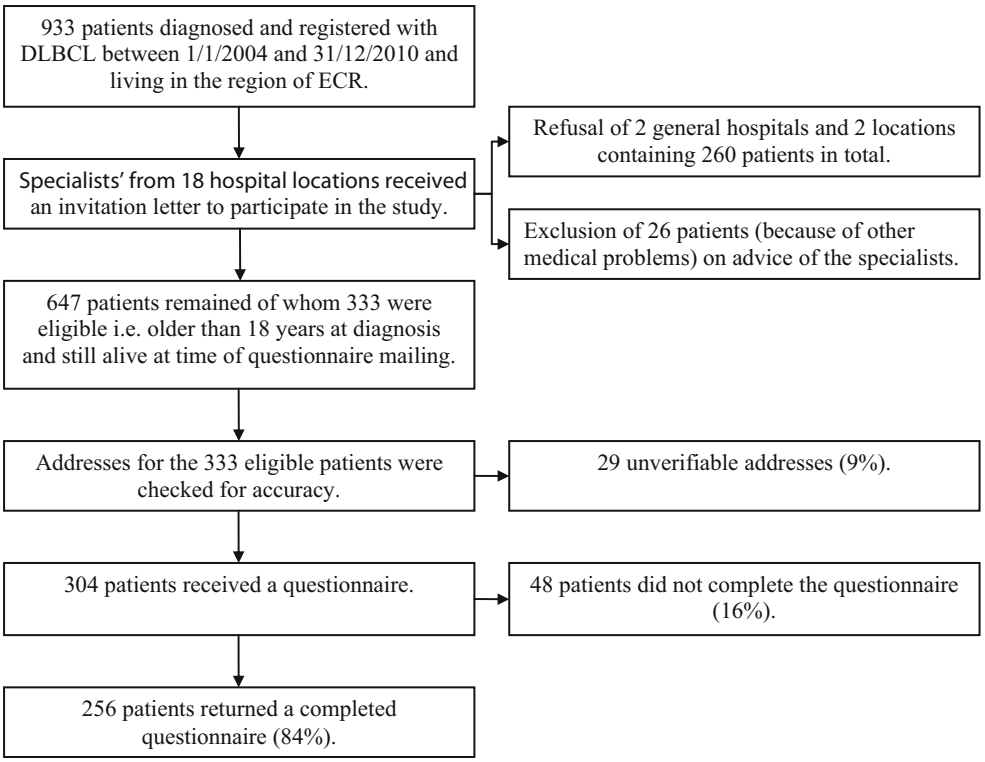

Fig. 1 Flow chart of the data collection process. *DLBCL* diffuse large B-cell lymphoma, *ECR* Eindhoven Cancer Registry

(R-)CHOP14 was received by 37 % and (R-)CHOP21 by 50 % of patients, the other 13 % was treated with SCT, HDCT, other, or no therapy. Two third of patients reported one or more comorbid conditions, the most common were arthritis, back pain, and hypertension. Patients treated with (R-)CHOP21 were older, more often diagnosed with stage I, and had a longer time since diagnosis and time since treatment compared to patients treated with (R-)CHOP14.

With respect to the age- and sex-matched normative population, mean age at baseline survey completion was 63.7 years, and 66 % was men. Almost two third (66 %) of respondents reported one or more comorbid conditions, the most common were hypertension and back pain.

Quality of data

Nonresponse analysis

At baseline, nonrespondents (N=48) and patients with unverifiable addresses (N=29) were more often female than respondents (60 and 66 % vs 34 %; $p<0.01$), and nonrespondents were more often treated shorter than 12 months ago compared to respondents (48 vs 27 %; $p=0.01$). No statistically significant differences between these groups were observed for age, time since diagnosis, stage, treatment, and number of treatment lines (data not shown).

Analysis between patients who completed one or more questionnaires

No statistically significant differences were observed between patients who completed one and patients who completed two questionnaires for QLQ-C30 global health and QoL score ($\overline{X}$ = 74.8 vs $\overline{X}$=72.9; $p=0.47$) or for sex, age, stage, (time since) treatment, comorbidities, marital status, and educational level (data not shown).

HRQoL of DLBCL patients and the normative population

Compared to an age- and sex-matched normative population, responding DLBCL patients exhibited on average statistically significant and clinically relevant worse scores on QLQ-C30 physical, role, cognitive, and social functioning. DLBCL patients also reported more fatigue, dyspnea, sleeping problems, appetite loss, and financial problems compared to the matched norm (all $p<0.05$ and small clinically important differences; Fig. 2).

HRQoL and symptoms/worries in relation to treatment

Patients treated with (R-)CHOP14 reported significantly more often tingling in hands and feet compared to patients treated with (R-)CHOP21 (42 vs 27 %, $p=0.02$; adjusted for age, number of comorbidities, time since treatment, and number of treatment cycles). Patients treated with (R-)CHOP14 also

Table 1 Clinical and sociodemographic characteristics of the total group of responding patients (*N*=256) and according to treatment regimen

	Total(*N*=256) Number (%)	Patients treated with HDCT±ASCT, other CT, RT, or no therapy (*N*=33) Number (%)	Patients treated with (R-)CHOP14 (*N*=95) Number (%)	Patients treated with (R-)CHOP21 (*N*=128) Number (%)	(R-)CHOP14 versus (R-)CHOP21 *p* value
Gender					0.80
Male	169 (66)	26 (79)	60 (63)	83 (65)	
Female	87 (34)	7 (21)	35 (37)	45 (35)	
Age: mean (SD)	63.5 (13.4)	56.5 (15.1)	61.4 (13.2)	66.9 (12.0)	<0.01
<5 years	58 (23)	12 (36)	26 (27)	20 (16)	
55–65 years	70 (27)	12 (36)	27 (28)	31 (24)	
66–75 years	87 (34)	7 (21)	34 (36)	46 (36)	
75+years	41 (16)	2 (6)	8 (8)	31 (24)	
Years since diagnosis at time of questionnaire completion: mean (SD)	2.6 (1.3)	2.8 (1.5)	2.0 (1.1)	2.9 (1.2)	<0.01
Months since treatment at time of questionnaire completion: median	21.0	24.0	16.3	29.2	<0.01
0–24 months since treatment	131 (51)	12 (36)	64 (67)	55 (43)	
24+months since treatment	112 (44)	11 (33)	29 (31)	72 (56)	
Missing	13 (5)	10 (30)	2 (2)	1 (1)	
Number of treatment lines					0.16
First treatment line	228 (89)	14 (42)	91 (96)	123 (96)	
Subsequent treatment line	17 (7)	8 (24)	4 (4)	5 (4)	
Missing	11 (4)	11 (33)	0 (0)	0 (0)	
Number of treatment cycles					<0.01
<6 cycles	NA	NA	12 (13)	35 (27)	
≥6 cycles	NA	NA	82 (86)	92 (72)	
Missing			1 (1)	1 (1)	
Stage at diagnosis					<0.01
I	85 (33)	15 (45)	15 (16)	55 (43)	
II	60 (23)	6 (18)	21 (22)	33 (26)	
III	56 (22)	6 (18)	31 (33)	19 (15)	
IV	53 (21)	6 (18)	26 (27)	21 (16)	
Missing	2 (1)	0 (0)	2 (2)	0 (0)	
Self-reported comorbidities					0.45
None	79 (31)	15 (45)	30 (32)	34 (27)	
1 comorbidity	83 (32)	9 (27)	32 (34)	42 (33)	
2 or more comorbidities	77 (30)	8 (24)	25 (26)	44 (34)	
Missing	17 (7)	1 (3)	8 (8)	8 (6)	
Marital status					0.87
Partner	201 (79)	25 (76)	76 (80)	100 (78)	
No partner	51 (20)	8 (24)	18 (19)	25 (20)	
Missing	4 (2)	0 (0)	1 (1)	3 (2)	
Education level					0.12
Low	41 (16)	2 (6)	14 (15)	25 (20)	
Medium	151 (59)	19 (58)	53 (56)	79 (62)	
High	60 (23)	11 (33)	27 (28)	22 (17)	
Missing	4 (2)	1 (3)	1 (1)	2 (2)	

In the (R-)CHOP14 group, 2 patients were treated without rituximab, and in the (R-)CHOP21 group, 15 patients were treated without rituximab. Education levels included low, no/primary school; medium, lower general secondary education/vocational training; or high, pre-university education/high vocational training/university

HDCT high-dose chemotherapy, *ASCT* autologous stem cell transplantation, *CT* chemotherapy, *RT* radiotherapy, (R-)CHOP=(Rituximab), cyclophosphamide, doxorubicin, vincristine, and prednisone, *NA* not applicable

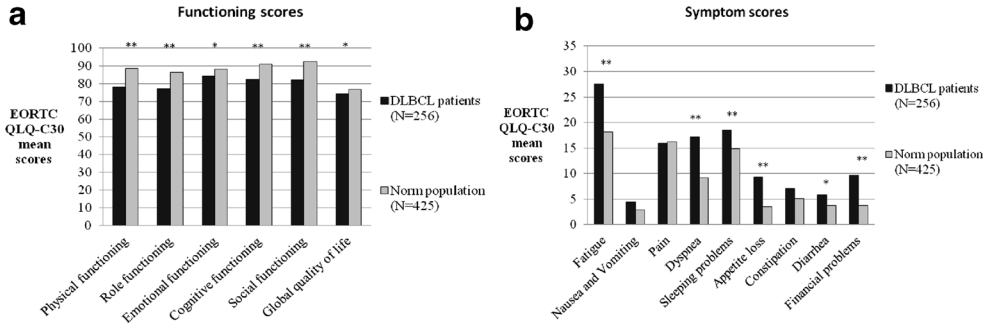

Fig. 2 Differences on EORTC QLQ-C30 mean functioning, global quality of life, and symptom scores between DLBCL patients (N=256) and an age- and sex-matched normative population (N=425). *p<0.05, **p<0.05 and small clinically important differences [21]. A higher score on functioning scores implies a better health-related quality of life, whereas a higher score on symptom scores refers to more symptoms. *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core30. *DLBCL* diffuse large B-cell lymphoma

reported a statistically significant lower global health status/quality of life compared to patients treated with (R-)CHOP21 (p=0.04; Table 2). Furthermore, significantly more patients with fatigue were identified in the (R-)CHOP14 group (46 %) compared to the (R-)CHOP21 group (35 %; p=0.03), and patients treated with (R-)CHOP14 also more often felt slowed down compared to patients treated with (R-)CHOP21 (44 vs 37 %; p=0.03). No statistically significant differences were observed on the other HRQoL scales and symptoms. HRQoL scores and percentages of symptoms/worries of patients treated with HDCT, ASCT, and other therapies are also displayed in Table 2, although numbers were too small to draw conclusions.

Prevalence of symptoms/worries

The most frequently reported symptoms/worries (by at least one third of patients) on T1 were worry about future health (53 %), skin problems (itching and dry skin; 42 %), feeling slowed down (40 %), dry mouth (40 %), and tingling in hands and feet (33 %). The prevalence of symptoms/worries did not significantly differ per time since treatment category, except for skin problems which occurred more often among patients who received treatment more than 3 years ago (Fig. 3). Furthermore, worry about future health and having a dry mouth seemed to occur more often among patients until 1 year after treatment.

Factors associated with persistent symptoms/worries and the relation with HRQoL

Of the patients who completed the questionnaire again 1 year later (N=130), persistent symptoms/worries were reported by 20–33 % of patients. Multivariate logistic regression analyses showed that older patients and patients treated with (R-)CHOP14 more often had persistent tingling in hands and feet compared to patients treated with (R-)CHOP21 independently of the other characteristics. Persistent worry about future health and a persistent slowed down feeling were reported more often by patients with comorbid diseases (Table 3). Persistent skin problems more often occurred among patients diagnosed longer ago. Sex, disease stage, and number of treatment cycles were not associated with any of the persistent symptoms/worries. Although it seemed that, when studying the crude percentages, after the eighth cycle of (R-)CHOP14, patients would report tingling in hands and feet more often compared to patients treated with less cycles (48 vs 32 %), and for patients treated with (R-)CHOP21 the percentages were 30 versus 25 %.

Subsequently, patients who reported to be persistently slowed down, worrying about future health, or having tingling hands or feet had statistically, significantly, and clinically relevant lower EORTC global health status/HRQoL compared to patients without these persistent symptoms/worries (all p<0.01, data not shown).

Discussion

HRQoL was lower among DLBCL patients compared to an age- and sex-matched normative population, which confirms our hypothesis. Patients treated with (R-)CHOP14 reported tingling in hands and feet, fatigue, and slowed down feeling more often compared to patients treated with (R-)CHOP21. Patients treated with (R-)CHOP14 also reported a lower global health status/quality of life compared to patients treated with (R-)CHOP21. The five most frequently reported symptoms/worries by at least one third of patients were worry about future health, skin problems, feeling slowed down, having a dry mouth, and having tingling in hands/feet. Subsequently, patients reporting one of these symptoms/worries exhibited significantly lower global health status/HRQoL compared to patients without these symptoms/worries.

Table 2 Differences between DLBCL patients treated with (R-)CHOP14, (R-)CHOP21, ASCT, HDCT, or other CT, RT, or no therapy on EORTC symptoms, worries, and HRQoL at T1

	Patients treated with (R-)CHOP14 (*N*=95)	Patients treated with (R-)CHOP21 (*N*=128)	(R-)CHOP14 versus (R-)CHOP21	Patients treated with HDCT ± ASCT, other CT, RT, or no therapy (*N*=33)
EORTC CLL-16	Number (%)	Number (%)	*p* value	Number (%)
Weight loss	18 (19)	16 (13)	0.29	3 (9)
Dry mouth	40 (42)	47 (38)	0.12	15 (47)
Bruises	8 (8)	9 (7)	0.86	4 (12)
Abdominal discomfort	31 (33)	40 (32)	0.94	8 (25)
Temperature up/down	14 (15)	16 (13)	0.91	2 (6)
Night sweats	27 (29)	44 (35)	0.58	8 (24)
Skin problems	37 (39)	55 (44)	0.66	15 (45)
Feeling ill or unwell	23 (24)	17 (13)	0.08	4 (12)
Feeling lethargic	33 (35)	39 (31)	0.08	8 (24)
Feeling slowed down	42 (44)	47 (37)	0.03	13 (39)
Limited in activities	32 (34)	37 (30)	0.15	12 (36)
Worried future health	55 (58)	60 (48)	0.05	20 (60)
Chest infections	14 (15)	19 (15)	0.17	9 (27)
Other infections	13 (14)	22 (17)	0.38	3 (9)
Repeated antibiotics	12 (13)	21 (17)	0.68	4 (12)
Worried about infections	22 (24)	27 (21)	0.62	9 (27)
Tingling hands/feet	40 (42)	34 (27)	0.02	9 (28)
EORTC QLQ-C30	Mean (SD)	Mean (SD)	*p* value	Mean (SD)
Physical functioning	76.9 (22)	78.9 (21)	0.21	79.6 (23)
Role functioning	75.1 (30)	79.4 (28)	0.16	73.2 (32)
Emotional functioning	82.7 (19)	85.9 (19)	0.20	81.8 (22)
Cognitive functioning	82.6 (23)	84.8 (20)	0.13	73.2 (28)
Social functioning	80.7 (26)	84.4 (25)	0.21	77.3 (31)
Global health status/QoL	71.9 (22)	75.2 (19)	0.04	76.0 (18)
Fatigue	28.2 (27)	26.5 (26)	0.25	29.5 (27)
Nausea/vomiting	5.6 (14)	4.1 (13)	0.55	2.5 (7)
Pain	18.4 (27)	14.4 (24)	0.22	14.1 (24)
Dyspnea	17.7 (28)	17.3 (26)	0.43	14.6 (22)
Insomnia	18.9 (29)	18.8 (29)	0.44	17.1 (22)
Appetite loss	13.0 (28)	8.6 (22)	0.19	1.0 (6)
Constipation	8.4 (23)	6.9 (19)	0.05	4.0 (14)
Diarrhea	7.4 (20)	5.6 (15)	0.13	2.0 (8)
Financial problems	11.9 (22)	5.9 (17)	0.09	18.1 (32)
% fatigued patients	46 %	35 %	<0.01	44 %

p value is adjusted for age, time since treatment, number of treatment cycles, and number of comorbidities. EORTC CLL16 symptoms/worries were dichotomized as present (answer categories "a bit," "quite a bit," or "very much") or not present (answer category "not at all"). Patients were fatigued if they had an EORTC QLQ-C30 fatigue score >23.1 (mean normative population + small clinically important difference, i.e., five points)

HDCT high-dose chemotherapy, *ASCT* autologous stem cell transplantation, *CT* chemotherapy, *RT* radiotherapy, *(R-)CHOP* (rituximab), cyclophosphamide, doxorubicin, vincristine, and prednisone, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core30, *DLBCL* diffuse large B-cell lymphoma, *CLL-16* chronic lymphocytic leukemia 16

Our results are in line with other studies comparing HRQoL between lymphoma patients and a normative population [22–25], whereby physical functioning, appetite loss, fatigue, and financial problems were most often affected. In the present study, also DLBCL patients treated >2 years ago were included, indicating that HRQoL is not only diminished at time of treatment but also thereafter.

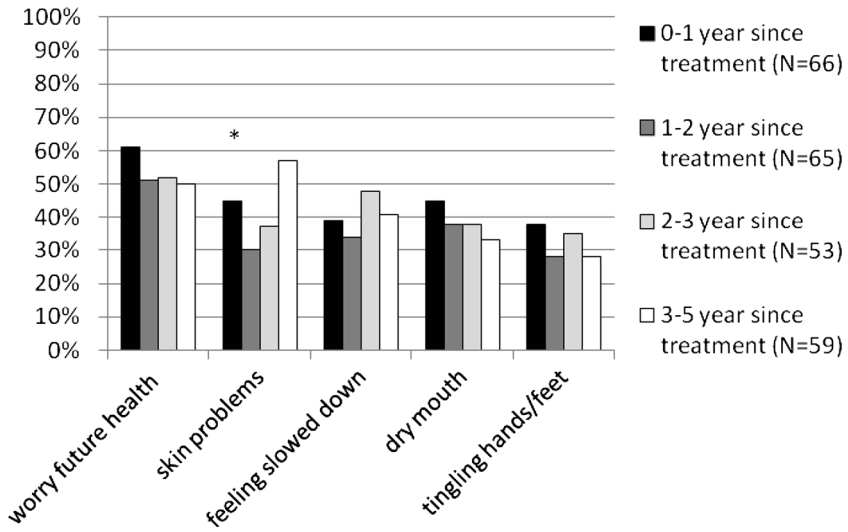

Fig. 3 Prevalence of worries and symptoms among DLBCL patients treated with (R-)CHOP14 (A) or (R-)CHOP21 (B) according to time since last treatment at T1. *DLBCL* diffuse large B-cell lymphoma. (*R-*)*CHOP*=(rituximab), cyclophosphamide, doxorubicin, vincristine, and prednisone

Experiences of neuropathy among lymphoma patients were also observed by two other studies, although they did not compare patients treated with (R-)CHOP14 versus (R-)CHOP21. One small longitudinal study among 32 B-cell lymphoma patients treated with (R-)CHOP or (R-)CVP observed sensory neuropathy-associated symptoms among 84 % and polyneuropathy among 44 % of patients [26]. The other longitudinal study observed a significant increase in peripheral neuropathy after the sixth cycle of CHOP compared to baseline [11]. We observed no statistically significant difference in tingling hands and feet according to the number of treatment cycles. Although it seemed that, when studying the crude percentages, after the eighth cycle of (R-)CHOP14, patients would report tingling in hands and feet more often compared to patients treated with less cycles. Further research should take this into account. An explanation for more neuropathy complaints among patients treated with (R-)CHOP14 might be that these patients receive vincristine (whereby neuropathy is a known side effect) in a quicker succession compared to patients treated with (R-)CHOP21.

An explanation for the higher fatigue prevalence among the (R-)CHOP14 group compared to the (R-)CHOP21 group (47 % versus 35 %) is likely to be the higher toxicity and/or intensity of the (R-)CHOP14 treatment.

Patients who had comorbid diseases, were diagnosed longer ago, or were treated with (R-)CHOP14 more often reported at least one persistent symptom. Subsequently, patients experiencing any of these symptoms/worries reported lower HRQoL compared to patients without these symptoms/worries. Therefore, these symptoms should be screened for and alleviated when possible to enhance patients HRQoL.

The current study has some limitations: Unfortunately, we did not have HRQoL and symptom scores of patients before treatment. Additionally, we could not compare HRQoL among patients treated in second line (HDCT or/and ASCT) due to small numbers and patients were enrolled in the study at different times since treatment, and this time span was significantly different for patients treated with (R-)CHOP14 versus (R-)CHOP21. Although we controlled for time since treatment in the analysis, the variance in time since treatment between the two treatment groups remains an important point of concern. Furthermore, in the present study, neuropathy was only assessed with a single item. To better understand the prevalence and course of neuropathy, research with validated multi-item neuropathy questionnaires and/or nerve conduction tests is necessary. The strengths of our study are that we assessed HRQoL in a population-based setting that includes patients with comorbidities and elderly patients, resulting in a very representative group of DLBCL patients treated in daily practice. In addition, comparison with an age- and sex-matched normative population provides important information about the impact of cancer and its treatment beyond the natural aging process and the impact of comorbidities. Furthermore, we assessed patients twice, which provides important information about the persistence of symptoms over time.

To our knowledge, this is the first study that compared HRQoL outcomes between patients treated with (R-)CHOP14 and (R-)CHOP21. Patients treated with (R-)CHOP14 more often reported tingling in hands and feet, were more often fatigued, and had more often a slowed down feeling compared to patients treated with (R-)CHOP21. They furthermore reported a lower global health status/HRQoL. Based on these findings with respect to HRQoL, (R-)CHOP21 seems the preferred treatment in DLBCL patients. In addition, clinicians

Table 3 Sociodemographic and clinical factors associated with five major persistent symptoms or worries among DLBCL patients (*N*=130)

	Persistent tingling hands/feet			Persistent worry future health			Persistent skin problems			Persistent slowed down feeling			Persistent dry mouth		
	Odds ratio	95 % CI	*p* values	Odds ratio	95 % CI	*p* values	Odds ratio	95 % CI	*p* values	Odds ratio	95 % CI	*p* values	Odds ratio	95 % CI	*p* values
Sex (men = ref)	0.50	0.2–1.5	0.22	1.37	0.6–3.2	0.46	0.83	0.3–2.0	0.67	2.23	0.9–5.6	0.09	1.78	0.8–4.1	0.18
Age	1.08	1.0–1.1	0.02	0.98	0.9–1.0	0.33	0.99	0.95–1.0	0.79	0.97	0.9–1.0	0.14	1.03	0.99–1.1	0.13
Time since diagnosis	1.42	0.9–2.1	0.09	1.01	0.7–1.4	0.95	1.51	1.1–2.1	0.02	1.12	0.8–1.6	0.54	0.99	0.7–1.3	0.96
Comorbidity (no=ref)	1.42	0.4–5.1	0.59	4.44	1.4–14	0.01	2.14	0.7–6.3	0.17	7.99	1.6–40	0.01	1.11	0.4–3.0	0.84
Stage															
Stage I	Ref			Ref			Ref			Ref			Ref		
Stage II	4.13	0.9–19.1	0.07	1.90	0.7–5.5	0.24	0.97	0.3–3.0	0.96	0.54	0.1–2.0	0.35	1.04	0.4–3.0	0.94
Stage III	3.51	0.7–18.4	0.14	0.44	0.1–1.6	0.20	2.36	0.7–7.6	0.15	0.50	0.1–1.9	0.32	0.88	0.3–2.9	0.84
Stage IV	3.72	0.8–17.8	0.10	1.04	0.3–3.2	0.95	0.56	0.2–2.0	0.38	0.90	0.3–3.1	0.87	1.46	0.5–4.5	0.51
Treatment															
(R-)CHOP14	4.29	1.3–14.5	0.02	0.95	0.3–2.6	0.93	2.02	0.7–6.0	0.20	1.01					
	0.3–3.0	0.99	1.83	0.7–4.9	0.23										
(R-)CHOP21	Ref			Ref			Ref			Ref			Ref		
Other	0.47	0.05–4.8	0.52	1.47	0.4–5.7	0.58	0.97	0.2–4.2	0.97	0.25	0.03–2.2	0.21	1.54	0.4–6.1	0.54

Other treatment category consists of patients treated with HDCT, ASCT, other CT, RT, or no therapy. Persistent symptoms were defined as a symptom which was present on both T1 and T2. We rerun the analyses with a number of treatment cycles instead of treatment or instead of stage. These analyses did not show any statistically significant associations between treatment cycles or stage and any of the persistent symptoms. Therefore, this model is not presented in a table

CI confidence interval, *Ref* reference category, *DLBCL* diffuse large B-cell lymphoma, *(R-)CHOP* (rituximab), cyclophosphamide, doxorubicin, vincristine, and prednisone

should be alert for symptoms that occur among DLBCL patients even long after diagnosis, as these symptoms have a negative influence on their HRQoL.

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References

1. Howlader N, Noone AM, Krapcho M et al (2013) SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, 2013, assessed on August 2013
2. Dutch Cancer Society (2011) Cancer in the Netherlands until 2020, trends and prognoses [Kanker in Nederland tot 2020, Trends en prognoses]
3. Coiffier B, Lepage E, Briere J et al (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235–242
4. Lossos IS (2005) Molecular pathogenesis of diffuse large B-cell lymphoma. J Clin Oncol 23:6351–6357
5. Fisher RI, Gaynor ER, Dahlberg S et al (1993) Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002–1006
6. Feugier P, Van Hoof A, Sebban C et al (2005) Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 23:4117–4126
7. Pfreundschuh M, Trumper L, Osterborg A et al (2006) CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 7:379–391
8. Pfreundschuh M, Trumper L, Kloess M et al (2004) Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 104:634–641
9. Cunningham D, Hawkes EA, Jack A et al (2013) Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 381:1817–1826
10. Delarue R, Tilly H, Mounier N et al (2013) Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. Lancet Oncol 14:525–533
11. Doorduijn J, Buijt I, Holt B et al (2005) Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy. Eur J Haematol 75:116–123
12. Jerkeman M, Kaasa S, Hjermstad M et al (2001) Health-related quality of life and its potential prognostic implications in patients with aggressive lymphoma: a Nordic Lymphoma Group Trial. Med Oncol 18:85–94
13. Merli F, Bertini M, Luminari S et al (2004) Quality of life assessment in elderly patients with aggressive non-Hodgkin's lymphoma treated with anthracycline-containing regimens.Report of a prospective study by the Intergruppo Italiano Linfomi. Haematologica 89:973–978
14. Heutte N, Haioun C, Feugier P et al (2011) Quality of life in 269 patients with poor-risk diffuse large B-cell lymphoma treated with rituximab versus observation after autologous stem cell transplant. Leuk Lymphoma 52:1239–1248
15. Jung HA, Park S, Cho JH et al (2012) Prognostic relevance of pretreatment quality of life in diffuse large B-cell lymphoma patients treated with rituximab-CHOP: results from a prospective cohort study. Ann Hematol 91:1747–1756
16. Fritz A, Percy C, Jack A et al (2000) International classification of diseases for oncology (ed 3rd). World Health Organisation, Geneva
17. van de Poll-Franse LV, Horevoorts N, Eenbergen MV et al (2011) The patient reported outcomes following initial treatment and long term evaluation of survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer
18. Aaronson NK, Ahmedzai S, Bergman B et al (1993) The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376
19. Sangha O, Stucki G, Liang MH et al (2003) The self-administered comorbidity questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 49:156–163
20. van de Poll-Franse LV, Mols F, Gundy CM et al (2011) Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. Eur J Cancer

21. Cocks K, King MT, Velikova G et al (2011) Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 29:89–96
22. Jensen RE, Arora NK, Bellizzi KM et al (2013) Health-related quality of life among survivors of aggressive non-Hodgkin lymphoma. Cancer 119:672–680
23. Mols F, Aaronson NK, Vingerhoets AJ et al (2007) Quality of life among long-term non-Hodgkin lymphoma survivors: a population-based study. Cancer 109:1659–1667
24. Reeve BB, Potosky AL, Smith AW et al (2009) Impact of cancer on health-related quality of life of older Americans. J Natl Cancer Inst 101:860–868
25. Smith SK, Zimmerman S, Williams CS, Zebrack BJ (2009) Health status and quality of life among non-Hodgkin lymphoma survivors. Cancer 115:3312–3323
26. Kim BJ, Park HR, Roh HJ et al (2010) Chemotherapy-related polyneuropathy may deteriorate quality of life in patients with B-cell lymphoma. Qual Life Res 19:1097–1103

Authorship and disclosures

All authors contributed to the conception and design of this paper; SO, DEI, and LVP wrote the paper, all other authors revised the paper critically for important intellectual content; SO, FM, and MRN recruited the patients; DEI, EGB, JWC, and PH collected the clinical data; SO and EGB performed the statistical analysis; LVP was the principal investigator and takes primary responsibility for the paper.

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