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Comorbidity is an independent prognostic factor in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP: a population-based cohort study

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Summary

An observational population-based cohort study was performed to investigate the role of comorbidity on outcome and treatment-related toxicity in patients with newly diagnosed advanced-stage diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). Data for the clinical characteristics of 154 patients (median age 69 years), including Charlson Comorbidity Index (CCI), treatment, toxicity and outcome were evaluated. Forty-five percent of the patients had an International Prognistic index ≥3 and 16% had a CCI ≥2. The planned R-CHOP schedule was completed by 84% and 75% reached complete remission (CR). In those with CCI ≥2, 67% completed treatment with 46% CR. In patients with a CCI <2, overall survival (OS) after 1, 2 and 5 years was 84%, 79% and 65% respectively and it was 64%, 48% and 48% for those with CCI ≥2. Grade III/IV toxicity was documented in 53%, most frequently febrile neutropenia (27%) and infections (23%). In multivariate analysis CCI ≥2 and IPI ≥3 were independent risk indicators for OS and grade III/IV toxicity. In conclusion, comorbidity is an independent risk indicator for worse OS in patients with advanced DLBCL treated with R-CHOP by interference with intensive treatment schedules and more grade III/IV toxicity. Future studies are warranted to determine the optimal treatment approach in patients with significant comorbidities.

Keywords: diffuse large B-cell lymphoma, comorbidity, population-based, toxicity, R-CHOP.

Diffuse large B-cell lymphoma (DLBCL) is predominantly diagnosed in the elderly and its incidence is rapidly increasing. Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the standard treatment for patients with newly diagnosed DLBCL (Coiffier *et al*, 2002). This is based on data from randomized controlled trials (RCT) with strict eligibility criteria, often excluding older patients and patients with significant comorbidity. More than 50% of patients with DLBCL have one or more coexistent diseases at the time of diagnosis (van Spronsen *et al*, 1999). Thus, in the real world, the presence of comorbidity may influence decision-making in daily clinical practice. For example, these patients may be more vulnerable for additional treatment-related toxicity resulting in impaired outcome (van Spronsen *et al*, 1999). Previous studies have shown that comorbidity can be regarded as an

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independent prognostic factor in several types of solid and lymphoproliferative malignancies (Piccirillo *et al*, 2004; Read *et al*, 2004; Janssen-Heijnen *et al*, 2005a) but real world data in patients with DLBCL treated with R-CHOP are scarce. We conducted a long-term, prospective, observational, population-based cohort study to assess the presence of comorbidity, treatment-related toxicity and outcome in patients with newly diagnosed advanced-stage DLBCL treated with R-CHOP with curative intent.

Patients and methods

Background

Starting in 2005, all patients from the five medical centres in Friesland, a province in the Northern part of the Netherlands with 650 000 inhabitants, diagnosed with a haematological malignancy were prospectively registered in HemoBase (http://www.hemobase.eu/) for objective assessment of clinical parameters and for research purpose. HemoBase is a web-based, multidisciplinary, population-based electronic health record specifically designed by professionals for haemato-oncology. With direct registration by professionals, involved in the diagnostic work-up and treatment, the database is representative for the incidence, characteristics and treatment of patients with a haematological malignancy in the complete Friesland area (Hoogendoorn *et al*, 2009).

Approval was obtained from the Medical Ethics Review Committee from Medical Centre Leeuwarden for this observational study. Informed consent was waived in accordance with Dutch regulations.

Study design and patient identification

This is a prospective, observational population-based cohort study examining treatment characteristics and outcomes for patients 18 years or older with advanced-stage DLBCL (Ann Arbor stage II–IV) who received at least one cycle of R-CHOP during a 7-year follow-up period between 1 January 2005 and 31 January 2012.

All relevant data regarding the clinical characteristics, laboratory tests, treatment and adaptations in chemotherapy, treatment-related toxicity and outcome were retrieved from HemoBase database and local patient records. Comorbidity data at time of diagnosis was collected retrospectively and scored by using the Charlson Comorbidity Index (CCI) (Charlson *et al*, 1987). A high comorbidity score was defined as CCI $\geq$2. The International Prognostic Index (IPI) was calculated for every patient. The histological diagnoses were made on the first nodal or extranodal biopsy according to the World Health Organization classification (Swerdlow *et al*, 2008). All histological diagnoses were reviewed by a panel of three experienced haematopathologists. To ensure that all diagnoses of DLBCL were captured, the HemoBase dataset was compared with the National Cancer Registry and no discrepancies were found. Clinical information was retrievable on more than 99% of the patients identified by the initial search. Patients with transformation from another lymphoma into DLBCL and patients with recurrent DLBCL were excluded.

Treatment and toxicity

Patients received either R-CHOP-21 or R-CHOP-14 chemotherapy in 6 or 8 cycles. Administration of granulocyte colony-stimulating factor (G-CSF) as either primary or secondary prophylaxis was registered. The decision for a particular treatment schedule and the adaptations during therapy were left to the discretion of the clinician. Dose reduction, defined as more than 20% reduction of cyclophosphamide and/or doxorubicin, from the standard regime was retrieved from HemoBase. The relative dose intensity (RDI) was defined as the actual dose intensity achieved by a patient relative to the planned dose intensity for the intended chemotherapy schedule and did not include vincristine and prednisone. All grade III/IV treatment-related toxicity was obtained from the hospital files and classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf). Toxicity was categorized in the following subgroups: febrile neutropenia (FN) and infections, venous thromboembolism (VTE), haematological toxicity (anaemia, thrombocytopenia and neutropenia other then FN), cardiotoxicity, pulmonary toxicity and other (including extravasation, renal and neurotoxicity).

Follow-up

Follow-up was completed until 31 January 2012. Tumour 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 criteria (Cheson *et al*, 2007). Recurrent or progressive disease was documented. For those patients whose outcome was not recorded in HemoBase, general practitioners were contacted about the current status. In case of death, causality with the disease or the received treatment was noted.

Statistical analysis

The primary end-point was overall survival (OS), defined as time of diagnosis until death by any cause. Survival was graphically depicted using the Kaplan–Meier method. Between-group differences were evaluated using the log-rank test for evaluating differences in OS. Cox proportional hazards modelling was used to identify significant risk indicators in OS and logistic regression to identify significant risk indicators for grade III/IV toxicity. In this, adjusted hazard ratios (HR) for OS and adjusted odds ratios (OR) for grade III/IV

Table I. Clinical characteristics.

Characteristics	No. of patients	Percentage (%)
Total group	154	
Gender		
Male	79	51
Female	75	49
Age		
<60 years	40	26
60–80 years	87	56
>80 years	27	18
WHO performance status		
0	69	48
1	56	39
2	12	8
3	7	5
Unknown	10	–
Ann Arbor stage		
2	49	32
3	39	25
4	66	43
Presence of B symptoms	42	27
Extranodal disease		
0	53	39
1	43	32
≥2	40	29
IPI		
0–1	36	26
2	38	28
3	35	26
4–5	26	19
Unknown	19	–
LDH		
<250 μ/l	64	42
≥250 μ/l	87	58
Unknown	3	–
CCI		
0	97	63
1	33	21
2	15	10
>2	9	6

WHO, World Health Organization; IPI, International Prognostic Index; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase.

toxicity with 95% confidence intervals and *P*-values were calculated.

Initially, univariate analyses were performed on *apriori* defined risk indicators as assessed in this study (Table I–III (where applicable)). These included the IPI and CCI. In addition, the underlying components were also evaluated by univariate analysis.

After univariate analysis, multivariate analysis employed a manual backward selection strategy, starting with the full model. This strategy was used to reduce the model to a final model with significant risk indicators at the level of $P < 0{\cdot}05$. In order to evaluate the individual effect of IPI and CCI, both IPI and CCI were evaluated as composite risk scores, without including the underlying components in the respective multivariate models.

Table II. Charlson comorbidity index.

Comorbidity	Score	No. of patients
Myocardial infarction	1	7
Congestive heart failure	1	4
Peripheral vascular disease	1	12
Cerebrovascular disease (except hemiplegia)	1	11
Dementia	1	0
Chronic pulmonary disease	1	9
Connective tissue disease	1	7
Ulcer disease	1	1
Mild liver disease	1	0
Diabetes (without complications)	1	21
Diabetes with end organ damage	2	0
Hemiplegia	2	0
Moderate or severe renal disease	2	1
Second solid tumour (non-metastatic)	2	7
Leukaemia	2	1
Lymphoma*	2	0
Moderate or severe liver disease	3	1
Second metastatic solid tumour	6	0
Acquired immunodeficiency syndrome	6	0

*Excluded from analysis.

Where applicable, differences between groups were evaluated by Fisher exact (for binary variables), Chi-square or Wilcoxon tests. A 2-tailed *P*-value <0·05 indicated statistical significance. All analyses were performed using commercially available computer software (Statistical Analysis System version 9.2, SAS Institute, Cary, NC, USA).

Results

Clinical characteristics

A total of 164 patients with advanced-stage DLBCL, who received at least one cycle of R-CHOP, were registered in the database during the study period. Seven patients were excluded because of incomplete data sets and 3 patients because of additional rituximab maintenance therapy. The clinical characteristics of the 154 patients analysed are shown in Table I. The median age was 69 years (range 23–93 years). Forty-five percent of the patients had an IPI ≥3 and in 37% at least one coexistent disease was found. A high CCI, defined as ≥2, was documented in 16%. Most frequently observed comorbidities for calculating CCI were diabetes mellitus and peripheral and cerebrovascular diseases (Table II).

Treatment and adaptations in therapy

The majority of the patients was treated with R-CHOP-21 and 67% achieved CR. The planned R-CHOP schedule was completed by 84%, with a CR of 75%. In those with a

Table III. Treatment and treatment outcome.

	All patients $N = 154$ *n* (%)	CCI <2 $N = 130$ *n* (%)	CCI ≥2 $N = 24$ *n* (%)
Treatment			
R-CHOP 14	41 (27)	37 (28)	4 (17)
R-CHOP 21	113 (73)	93 (72)	20 (83)
Number of R-CHOP cycles			
≥6	129 (84)	113 (87)	16 (67)
2–5	16 (10)	13 (10)	3 (12)
1	9 (6)	4 (3)	5 (21)
Radiotherapy	23 (15)	16 (12)	7 (29)
Relative dose intensity ≤80%			
Doxorubicin	9	5 (4)	4 (17)
Cyclophosphamide	1	0 (0)	1 (4)
Both	22	17 (13)	5 (21)
G-CSF use			
R-CHOP 14	41 (100)	37 (100)	4 (100)
R-CHOP 21	24 (16)	19 (20)	5 (25)
Response to treatment			
CR/CRu	101 (67)	90 (70)	11 (46)
PR	19 (12)	16 (12)	3 (13)
SD	3 (2)	1 (1)	2 (8)
PD	16 (10)	14 (11)	2 (8)
Death without progression	8 (5)	6 (5)	2 (8)
Unknown	7 (4)	3 (2)	4 (17)
Causes of death	46 (30)	34 (26)	12 (50)
Lymphoma	33 (22)	25 (19)	8 (33)
Side effects chemotherapy	9 (6)	6 (5)	3 (13)
Other diseases	2 (1)	1 (1)	1 (4)
Unknown	2 (1)	2 (2)	0 (0)

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor; CR, complete remission; CRu, unconfirmed complete remission; PR, partial response; SD, stable disease; PD, progressive disease; CCI, Charlson Comorbidity Index.

CCI ≥2, 67% finalized treatment and 46% reached a CR. All response rates are shown in Table III.

A RDI <80% in either cyclophosphamide or doxorubicin was found in 17% of patients with a CCI <2 and in 42% of those with a CCI ≥2 ($P = 0{\cdot}012$). All patients treated with R-CHOP-14 received G-CSF as part of supportive care. In those treated with R-CHOP-21, only 3 patients received G-CSF as pre-emptive prophylactic therapy. In another 21 patients, G-CSF was started as secondary prophylaxis because of the occurrence of FN in a previous cycle.

Treatment outcome

Median follow-up was 25 months (range 0–83 months) and, at the time of analysis, 46 patients died, of whom the majority of deaths was disease-related (Table III). Disease progression was documented in 16 patients. The majority of these patients (86%) proceeded with second line chemotherapy and only 5 patients received radiotherapy as treatment modality.

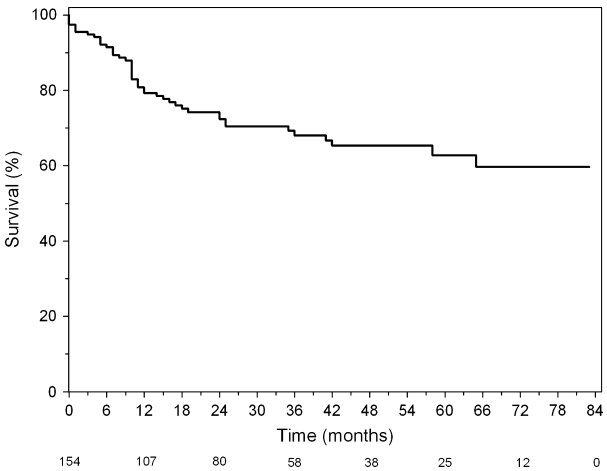

Fig 1. Overall Survival in the total patient population.

OS at one, two and 5 years was 81%, 74% and 63% respectively (Fig 1). In the univariate analysis, age (age >80 years: HR 3·67, 95%CI (1·46–9·22); $P = 0{\cdot}018$), IPI ≥3 (HR 2·31, 95%CI (1·20–4·74); $P = 0{\cdot}012$), CCI ≥2 (HR 2·24, 95%CI (1·17–4·30); $P = 0{\cdot}016$) were significantly associated with worse OS. In multivariate analysis CCI ≥2 (HR 3·09, 95%CI (1·55–6·15); $P = 0{\cdot}001$) and IPI ≥3 (HR 2·33, 95%CI (1·21–4·50); $P = 0{\cdot}011$) remained independent risk indicators for worse OS (Table IV). The OS of patients with a CCI <2 was superior to those with a CCI ≥2. The 1-, 2- and 5-year OS for the group with CCI <2 was 84%, 79% and 65% respectively, and it was 64%, 48% and 48% for those with CCI ≥2 (Fig 2).

Treatment-related toxicity

In 80 patients 139 grade III/IV treatment-related complications were recorded, predominantly FN and infections in 27% and 23% of the patients, respectively (Table V). FN occurred in 17% of patients treated with R-CHOP-14 and in 31% in those who received R-CHOP-21 ($P = 0{\cdot}10$). Infections were documented in 27% and 21%, respectively. Other toxicities are listed in Table V. Following univariate analysis, multivariate logistic regression analysis was performed including CCI ≥2 (HR 3·69 95%CI (1·23–11·08); $P = 0{\cdot}020$) and IPI ≥3 (HR 3·30 95%CI (1·59–6·84); $P = 0{\cdot}001$). In this analysis, both IPI and CCI were identified as independent riks indicators for grade III/IV toxicity (Table VI).

Toxicity-related deaths were observed in 9 patients, of whom 8 patients were older than 65 years and three had a CCI ≥2. The main cause of death was (neutropenic) sepsis in 6 patients; 2 died of pneumonia and 1 developed an ileus during treatment.

Discussion

This population-based cohort study prospectively followed all R-CHOP-treated patients with advanced-stage DLBCL for a

Table IV. Risk factors for overall survival.

	Univariate analysis		Multivariate analysis (final model)	
Risk factors	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age				
<60 years	1	0·018		
60–80 years	1·92 (0·83–4·42)			
>80 years	3·67 (1·46–9·22)			
Sex	1·55 (0·86–2·79)	0·146		
Ann-Arbor stage		0·72		
II	1			
III	0·91 (0·41–2·00)			
IV	1·21 (0·61–2·38)			
IPI			2·33 (1·21–4·50)	0·011
IPI <3	1			
IPI ≥3	2·24 (1·17–4·30)	0·016		
Extranodal disease	1·39 (0·71–2·73)	0·33		
LDH > normal	1·44 (0·79–2·65)	0·24		
CCI ≥2	2·31 (1·20–4·74)	0·012	3·09 (1·55–6·15)	0·001

IPI, International Prognostic Index; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; HR, Hazard Ratio; 95% CI, 95% confidence interval.

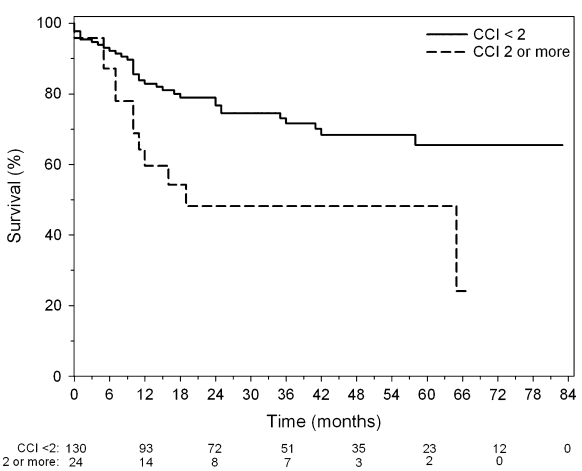

Fig 2. Overall survival in patients with Charlson Comorbidity Index (CCI) ≥2 compared with patients with CCI <2.

time period of 7 years in a well-defined area. In this unselected patient population comorbidity (CCI ≥2) and IPI ≥3 were independent risk indicators for OS. Grade III/IV treatment-related toxicity was documented in 53% of the patients and was more frequently observed in those with CCI ≥2 and with IPI ≥3.

Comorbidity as independent prognostic factor

As illustrated in our study and described in several types of cancer, comorbidity is an independent prognostic factor without correlation with functional status (Firat *et al*, 2002; Piccirillo *et al*, 2004; Read *et al*, 2004; Janssen-Heijnen *et al*, 2005a; van Spronsen *et al*, 2005). The CCI is the most frequently applied comorbidity score in studies and is validated in patients with cancer. A high CCI has been shown to be associated with impaired outcome (Singh *et al*, 1997; Extermann *et al*, 1998; Ouellette *et al*, 2004; Birim *et al*, 2005; Guzzo *et al*, 2010)). Several studies performed in aggressive non-Hodgkin lymphoma (NHL) patients, including a retrospective analysis in 80 elderly patients with DLBCL treated with R-CHOP, a population-based cohort study and a study with relapsed NHL treated with autologous stem cell transplantation, found that high CCI was independently associated with poor OS (Janssen-Heijnen *et al*, 2005b; Wildes *et al*, 2008; Kobayashi *et al*, 2011).

Table V. Treatment toxicity.

Item	*n* (%)
Patients with grade III/IV toxicity	80 (53)
Total number of events	139
Toxicity	
Febrile neutropenia	42 (27)
Infections	35 (23)
Venous thromboembolism	7 (5)
Cardiotoxicity	7 (5)
Pulmonary toxicity	3 (2)
Haematological toxicity	16 (10)
Other	18 (12)

Our analysis provides several potential explanations for the impaired outcome in DLBCL patients with significant comorbidities, treated with R-CHOP. First, a significantly lower percentage of patients with high CCI could complete the planned R-CHOP chemotherapy scheme compared with those without relevant comorbidities. Consequently, lower

Table VI. Risk factors for grade III/IV toxicity.

	Univariate analysis		Multivariate analysis (final model)	
Risk factors	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age				
<60 years	1	0·004		
60–80 years	3·15 (1·42–7·00)			
>80 years	5·25 (1·80–15·35)			
Sex	1·26 (0·67–2·38)	0·47		
Ann-Arbor stage		0·146		
II	1			
III	1·05 (0·45–2·45)			
IV	1·96 (0·93–4·17)			
IPI				
IPI <3	1			
IPI ≥3	3·24 (1·59–6·62)	0·001	3·30 (1·59–6·84)	0·001
Extranodal disease	1·50 (0·71–3·17)	0·29		
LDH > normal	2·66 (1·36–5·19)	0·004		
CCI ≥2	3·24 (1·21–8·69)	0·019	3·69 (1·23–11·08)	0·020

IPI, International Prognostic Index; CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; OR, odds ratio; 95% CI, 95% confidence interval.

response rates were reached and higher numbers of lymphoma-related deaths were observed in these patients. Second, although no differences in OS were seen between patients completing chemotherapy with a RDI ≥80% and those with a RDI <80% in one or more antineoplastic drugs, 42% of patients with a CCI ≥2 had a RDI <80% compared with 17% in patients with CCI <2. Whether these dose adaptations had an attributable incremental effect on disease progression, relapse and ultimately on OS remains speculative. In conclusion, we hypothesized that the presence of comorbidity may interfere with intensive treatment schedules, resulting in poor survival. An additional factor that may contribute to the negative influence on survival is the three times higher risk for toxicity in our patients with a high CCI.

OS in population-based studies

While RCTs often exclude patients with multiple comorbidities and/or advanced age, several (retrospective) population-based analyses showed the benefit of rituximab in unselected populations with DLBCL. The OS results in our patient population were in the same range reported in these studies (Sehn *et al*, 2005; Seki *et al*, 2010; Lee *et al*, 2012; Li *et al*, 2012). For example, our 2-year OS data were comparable with the study performed in British Colombia (74% and 78% respectively) (Sehn *et al*, 2005) and our 5-year OS was comparable with the population-based analysis of DLBCL patients treated with R-CHOP by Lee *et al* (2012) (65% vs. 62%). A retrospective study performed in China yielded higher 5-year OS data (84% vs. 62%) (Li *et al*, 2012). However, due to differences in inclusion criteria (e.g. inclusion of Ann Arbor stage I) and baseline patient characteristics (e.g. IPI), no direct comparison of outcomes between the studies can be performed.

Treatment-related toxicity

Grade III/IV toxicity was documented in one half of the patients and FN and infections were most frequently observed (27% and 23%, respectively). The rate of reported treatment-related toxicity of R-CHOP varies among previously published population-based studies, due to differences in baseline characteristics, the accuracy of documentation and the kind of reported toxicities (e.g. only hospitalization). A recently published analysis from the population-based DLBCL registry in Ontario, showed FN in 24·5% and infections in 3·5% of the patients treated with R-CHOP without extensive revisions of the clinical files, probably resulting in underreporting (Lee *et al*, 2012). A recent RCT in a preselected patient population comparing R-CHOP-21 with R-CHOP-14, reported 11% FN and 23% infections in patients in the R-CHOP-21 arm (Cunningham *et al*, 2013). In our unselected population, most grade III/IV toxicities regarding FN and infections were well documented in clinical files; only minor toxicities, such as neurotoxicity or mucositis may have been underreported due to irregularity in assessment. As described in clinical guidelines, patients treated with chemotherapy and a high risk (defined as >20%) for FN, should be considered candidates for primary prophylaxis with G-CSF (Aapro *et al*, 2011). The high rate of FN in our cohort treated with R-CHOP-21 suggests underuse of primary prophylaxis, as recently reported by others (Lugtenburg *et al*, 2012). Better adherence to the guidelines may prevent FN and, more importantly, may consequently prevent dose adaptations, thereby possibly improving clinical outcome.

Strengths and limitations

In the setting of population-based research this study has several strengths and weaknesses. The origin of this dataset, HemoBase, is a physician-initiated registry where all data are directly entered in the database by clinicians and other health-care professionals (e.g. from pathology and clinical chemistry). With all hospitals participating in this initiative these data are complete and representative for this region, without referral of these patients to tertiary institutions and therefore without the risk of selection bias. By prospectively gathering data on treatment, toxicity and long-term follow-up we acquired more insight in daily clinical practice in a unselected patient population outside the clinical trials. Hereby, we are able to show results from the real world and provide information that can contribute to the design of future trials (Boslooper *et al*, 2013).

However, our study has also several limitations when interpreting the results. The use of a real-life population, without patient selection, may affect the internal validity. For example, treatment strategies (such as dose reduction) relied on the clinical judgement of the physicians and the follow-up of patients was based on daily routine rather than a strictly protocolized follow-up. Furthermore, the calculation and interpretation of the CCI relied on the documentation of relevant comorbidity in the medical history by clinicians, with a risk of incomplete data. A multivariate analysis was performed to assess the independent influence of prognostic factors. However, the possibility of undocumented confounding factors cannot be ruled out.

Conclusion

In this population-based analysis of all patients with advanced-stage DLBCL treated with R-CHOP, comorbidity and IPI were independent risk indicators for worse OS and grade III/IV toxicity. Comorbidity interfered with intensive treatment schedules, resulting in a higher percentage of patients with incomplete treatment, more patients with dose adaptations of chemotherapy and was associated with more grade III/IV treatment-related toxicity. Future studies are warranted to determine the optimal treatment approach in patients with significant comorbidities.

Author contributions

K. Boslooper and A. Wieringa performed the research, collected and interpreted the data and wrote the manuscript. Mels Hoogendoorn designed and supervized the research study and is a member of the project team HemoBase. P. Joosten and H. Storm designed the research study and both are members of project team HemoBase. T. Beerden collected the data. R. Kibbelaar reviewed the histolopathological diagnosis, designed the study and is a member of project team HemoBase. G.J. Veldhuis, H. van Kamp and B. van Rees supervized the data collection. J.C. Kluin-Nelemans designed and supervized the research study. N. Veeger interpreted the data and performed the statistical analysis. E.N van Roon designed and supervized the research study and interpreted the data. All authors critically reviewed the manuscript and approved the submitted and final version.

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