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RESEARCH ARTICLE

R-miniCHOP versus R-CHOP in elderly patients with diffuse large B-cell lymphoma: A propensity matched population-based study

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Abstract

For elderly frail patients with diffuse large B-cell lymphoma (DLBCL), an attenuated chemo-immunotherapy strategy of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-miniCHOP) was introduced as a treatment option as from 2014 onward in the Netherlands. Although R-miniCHOP is more tolerable, reduction of chemotherapy could negatively affect survival compared to R-CHOP. The aim of this analysis was to assess survival of patients treated with R-miniCHOP compared to R-CHOP. DLBCL patients ≥65 years, newly diagnosed in 2014–2020, who received ≥1 cycle of R-miniCHOP or R-CHOP were identified in the Netherlands Cancer Registry, with survival follow-up through 2022. Patients were propensity-score-matched for baseline characteristics. Main endpoints were progression-free survival (PFS), overall survival (OS), and relative survival (RS). The use of R-miniCHOP in DLBCL increased from 2% in 2014 to 15% in 2020. In total, 384 patients treated with R-miniCHOP and 384 patients treated with R-CHOP were included for comparison (median age; 81 years, stage 3–4; 68%). The median number of R-(mini)CHOP cycles was 6 (range, 1–8). The 2-year PFS, OS and RS were inferior for patients treated with R-miniCHOP compared to R-CHOP (PFS 51% vs. 68%, $p < .01$; OS 60% vs. 75%, $p < .01$; RS 69% vs. 86%, $p < .01$). In multivariable analysis, patients treated with R-miniCHOP had higher risk of all-cause mortality compared to patients treated with R-CHOP (HR 1.73; 95%CI, 1.39–2.17). R-miniCHOP is effective for most elderly patients. Although survival is inferior compared to R-CHOP, the use of R-miniCHOP as initial treatment is increasing. Therefore, fitness needs to be carefully weighed in treatment selection.

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of mature B-cell lymphoproliferative disease.[1] Standard treatment for patients with DLBCL consist of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). The median age at diagnosis of patients with DLBCL receiving treatment is 68 years.[2] With aging, multiple physiological and homeostatic systems decline and comorbidity rises. As such, a significant portion of patients with DLBCL may be unable to tolerate the full dosage of R-CHOP.

For frail patients with DLBCL, overall indicated as patients of 80 years and older at baseline, an attenuated chemo-immunotherapy strategy of R-miniCHOP was introduced gradually as an alternative regimen in case of expected toxicity in the Netherlands from 2014 onwards. This regimen includes a near 50% reduction in the cumulative anthracycline and cyclophosphamide dosage, with additional dosage adjustments in vincristine and prednisolone.[3] Both the ESMO clinical practice guideline and NCCN guideline currently recommend R-miniCHOP in patients aged over 80 years.[4,5]

The 2-year overall survival (OS) of DLBCL patients >80 years treated with R-miniCHOP ranges from 59%–68%.[3,6,7] While R-miniCHOP is more tolerable, a direct comparison with R-CHOP is lacking. The clinical issue remains whether better tolerability of R-miniCHOP outweighs the possible higher incidence of treatment failures when compared to R-CHOP. Since a randomized clinical trial (RCT) addressing this question is unlikely to be performed, the study design closest to an RCT is a propensity-score-matched analysis using population-based data.

Therefore, the aim of this population-based study was to determine the efficacy of R-miniCHOP compared to R-CHOP on progression-free survival (PFS), OS, and relative survival (RS) in a propensity matched well annotated cohort of elderly patients (≥65 years) with DLBCL.

2 | MATERIALS AND METHODS

2.1 | Registry and study population

The nationwide, population-based Netherlands Cancer Registry (NCR) is maintained and hosted by the Netherlands Comprehensive Cancer Organization (IKNL) and covers >95% of all newly diagnosed malignancies since 1989 in the Netherlands.[8] Information on age, sex, date of diagnosis, topography, morphology, and first-line treatment are registered in the NCR. Since 2014, additional information on diagnostic and first-line treatment characteristics is registered, such as performance status, serum lactate dehydrogenase (LDH), number of nodal and extranodal localizations, bone marrow involvement, chemo-immunotherapy or other therapeutic regimen, and response to treatment. From 2017 onwards, imaging is registered in compliance with the Dutch guidelines. All information is retrospectively extracted from the medical records by trained registrars.

All patients with DLBCL, diagnosed between January 1, 2014 and December 31, 2020, were identified in the NCR, using the International Classification of Diseases for Oncology (ICD-O) of the World Health Organization (WHO) morphology codes 9680 and 9684. Patients ≥65 years who received at least 1 cycle of R-miniCHOP or R-CHOP were included. Patients with dose escalations from R-miniCHOP and dose reductions from R-CHOP were excluded (Figure S1). Survival follow-up was available through 1st February 2022. After this date, all patients alive were censored in the survival analysis.

According to the Central Committee on Research involving Human Subjects (CCMO), this type of observational study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

2.2 | Endpoints

The endpoints were overall response rate (ORR; best response is complete or partial remission), PFS, OS, and relative survival (RS). Best response was determined by physician assessment using the Lugano classification as of 2014 onward. PFS was defined as the time between diagnosis and relapse, refractory disease or death from any cause, which ever occurred first. OS was defined as the time between diagnosis and death from any cause. RS was defined as the ratio of the OS of the patient cohort to the expected OS of an equivalent group from the general population, matched by age and sex. As such, RS reflects the overall excess mortality associated with a DLBCL diagnosis, thereby estimating disease specific survival in the absence of information on the cause of death (COD). Therefore, RS is also useful to indirectly account for comorbidities, as RS represents the proportion of patients with DLBCL alive post-diagnosis at all times, which implies that these patients did not die from causes other than DLBCL at a specific time point.

2.3 | Propensity-score matching

To account for baseline differences between R-miniCHOP and R-CHOP 1:1 propensity-score matching was performed.[9] Caliper matching without replacement was applied for patients with R-miniCHOP and R-CHOP. With matching without replacement, any patient treated with R-CHOP was used once to match with a patient treated with R-miniCHOP. The variables age (as a continues variable), sex, Ann Arbor stage (stages I, II, III, and IV), International Prognostic Index (IPI) score (categories 0–1, 2–3, and 4–5) at baseline and type of treatment regimen (categories 6 cycles of chemoimmunotherapy, and 3 cycles of chemoimmunotherapy with subsequent radiotherapy) were matched by propensity scores within a caliper of 0.40 standard deviations of the propensity score. Radiotherapy was used as a proxy to distinguish between the two treatment regimens, for example, 3 cycles of

chemoimmunotherapy along with radiotherapy, and 6 cycles of chemoimmunotherapy, and therefore to equally distribute patients. Patients were excluded from matching if no matches were available with the same propensity score.

2.4 | Statistical analysis

Descriptive statistics were used to present patients and treatment characteristics. The Pearson chi-square test was used to compare categorical covariables, and the Kruskal-Wallis test was used to compare non-normally distributed continuous covariables between the two treatment groups.

ORR was calculated as the percentage of patients with complete or partial remission, in respect to the total cohort. PFS, OS, and RS were estimated according to the Kaplan–Meier method. Regarding PFS, patients diagnosed between 2014 and 2018 were actively followed up for occurrence of relapse, while patients diagnosed in 2019 or 2020 were not. As a consequence, only early relapses (within 1 year post-diagnosis) were known for patients diagnosed in 2019 or 2020. Therefore, patients diagnosed in 2019 or 2020 who were alive without relapse were censored at 1 year of follow-up. The log-rank test was used to evaluate differences in survival distributions. RS and 95% confidence intervals (CIs) were calculated as the OS divided by the expected survival (ES) of an equivalent population, using the Ederer II methodology from Dutch population life tables.[10]

The impact of age as a categorical variable (65–79 years, and 80 years or older), sex, serum LDH, WHO performance score, number of extranodal sites, Ann Arbor stage, and prior malignant disease as categorical variables, was evaluated, using uni- and multivariable Cox proportional hazard regression analysis. The results from the Cox regression analyses produce hazard ratios (HRs) with associated 95% CIs. All covariables with a significant difference in the univariable regression model were introduced in the multivariable regression model. Then, covariables were sequentially removed with the highest *p*-value above .05. The final model was accomplished when the *p*-value for excluding an additional covariable was above .05. Statistical analyses were performed using STATA/SE 17.0 (StataCorp LP, College Station, Texas, USA).

3 | RESULTS

In total, between 2014 and 2020 4234 DLBCL patients ≥65 years were treated with at least 1 cycle of R-CHOP; from these patients, 386 (9%) received R-miniCHOP. The use of R-miniCHOP increased from 2% in 2014 to 15% of all DLBCL patients ≥65 years in 2020 (Figure S2). The increased use of R-miniCHOP was primarily observed in patients >80 years, with a decline in the use of R-CHOP and other therapies. The majority of patients receiving R-miniCHOP were >75 years.

3.1 | Patient characteristics

Following matching, 2 patients who received R-miniCHOP were excluded due to no overlap of the propensity scores with patients who received R-CHOP. In total, 768 patients treated with R-miniCHOP and R-CHOP (384 patients in each arm) were included (Figure S1). The median age was 81 years (range, 65–94 years) with 67% of patients having an advanced stage disease. High-risk disease (IPI score ≥3) was present in 31% of patients. No significant differences in baseline characteristics were observed (Table 1).

3.2 | First-line therapy

The median number of cycles received was 6 (range, 1–8) for patients who received R-miniCHOP or R-CHOP regimens (Table 1). The application of abbreviated chemotherapy followed by radiotherapy was similar for patients treated with R-miniCHOP and R-CHOP 6% and 9%, respectively; $p = .17$). Radiotherapy was administered in 2 patients with bulky disease. In 35% of patients, the indication for radiotherapy was unknown. Among patients treated with R-miniCHOP, 9% received central nervous system (CNS) prophylaxis, compared to 14% treated with R-CHOP ($p = .06$).

3.3 | Outcome

The median follow-up was 35 months (inter quartile range [IQR], 12–57 months). Response assessment was determined with positron emission tomography/computed tomography (CT) scan in 79% of patients treated with R-miniCHOP compared to 88% treated with R-CHOP ($p = .02$), with the remainder of patients being evaluated by CT-scan alone. A significant difference in ORR was observed between patients treated with R-miniCHOP and R-CHOP (72% vs. 83%, respectively; $p < .01$; Figure 1). The CR rates in the R-miniCHOP and R-CHOP groups were 60% and 73%, respectively ($p < .01$). Primary refractory disease at end of treatment was observed in 5% and 3%, respectively ($p = .26$).

In total, relapse or progression was observed in 61 (16%) patients who received R-miniCHOP compared to 43 (11%) patients who received R-CHOP ($p = .06$). CNS relapse occurred in 11 (1%) patients, of whom 3 patients were treated with R-miniCHOP and 8 patients with R-CHOP ($p = .13$). Of the patients who relapsed after R-miniCHOP, 35% did not receive second-line treatment, compared to 36% who received R-CHOP as primary treatment. Among patients who received second-line treatment, the most common strategies were rituximab, prednisolone, etoposide, chlorambucil, and lomustine (R-PECC; 35% and 25%, respectively), and radiotherapy (14% and 22%, respectively).

The 2-year PFS estimate for patients treated with R-miniCHOP was inferior compared to patients treated with R-CHOP (51% vs. 68%, $p < .01$; Figure 2). The 2-year OS for patients treated with R-miniCHOP

TABLE 1 Characteristics of patients with a diffuse large B-cell lymphoma receiving R-miniCHOP or R-CHOP.

	R-miniCHOP	%	R-CHOP	%	*p*-value
N	384		384		
Male sex	190	(49)	192	(50)	.89
Age years—median (range)	81 (65–94)		81 (65–94)		.95
≥80 years					.76
No	124	(32)	128	(33)	
Yes	260	(68)	256	(67)	
Ann Arbor stage					.57
I–II	122	(32)	127	(33)	
III–IV	259	(67)	256	(67)	
Unknown	3	(1)	1	(0)	
Lactate dehydrogenase					.24
Normal	151	(39)	147	(38)	
Elevated	223	(58)	233	(61)	
Unknown	10	(3)	4	(1)	
WHO Performance score					.15
WHO 0–2	209	(54)	220	(57)	
WHO 3–4	31	(8)	18	(5)	
Unknown	144	(38)	146	(38)	
Number of extranodal sites					.32
0–1	273	(71)	264	(69)	
>1	103	(27)	116	(30)	
Unknown	8	(2)	4	(1)	
IPI-score					.86
Low (0–1)	46	(12)	44	(11)	
Intermediate (2–3)	112	(29)	123	(32)	
High (4–5)	107	(28)	101	(26)	
Unknown	119	(31)	116	(30)	
Prior malignant disease					.26
No	290	(76)	303	(79)	
Yes	94	(24)	81	(21)	
Number of cycles - median (range)	6 (1–8)		6 (1–8)		.09
Radiotherapy					.91
No	337	(88)	338	(88)	
Yes	47	(12)	46	(12)	
3 cycles of R-CHOP with radiotherapy					.17
No	360	(94)	350	(91)	
Yes	24	(6)	34	(9)	
CNS prophylaxis					.06
Intrathecal methotrexate	36	(9)	50	(13)	
High dose methotrexate	0	(0)	3	(1)	
No prophylaxis	348	(91)	331	(86)	

Abbreviations: CNS, central nervous system; IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; WHO, World Health Organization.

was significantly inferior compared to patients treated with R-CHOP (60% vs. 75%, $p < .01$; Figure 3). Moreover, the 2-year RS was inferior for patients treated with R-miniCHOP compared to patients treated with R-CHOP (69% vs. 86%, $p < .01$; Figure 4) In multivariable analysis, patients treated with R-miniCHOP had higher risk of relapse (HR 1.69; 95%CI, 1.36–2.10) and mortality (HR 1.74; 95%CI, 1.39–2.17) compared to patients treated with R-CHOP. Moreover, older age (≥80 years) negatively affected risk of relapse and mortality, as well as elevated serum LDH, WHO performance score ≥3, and >1 extranodal sites (Figure 5 and Table S1).

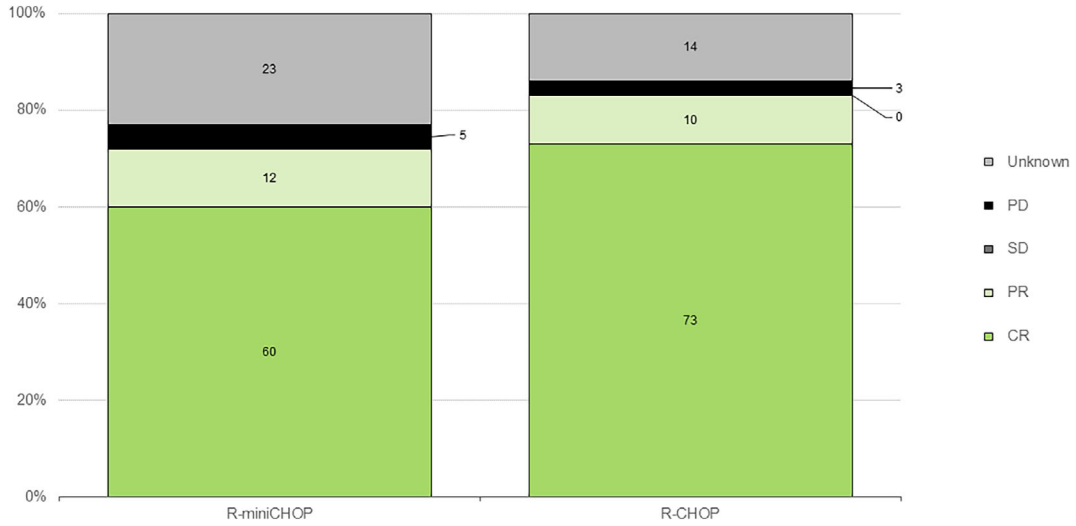

FIGURE 1 Best observed response in patients with diffuse large B-cell lymphoma treated with R-miniCHOP or R-CHOP. Stacked bar graph depicting best response showing a significant difference in overall response in patients treated with R-miniCHOP compared to patients treated with R-CHOP ($p < .01$). [Color figure can be viewed at wileyonlinelibrary.com]

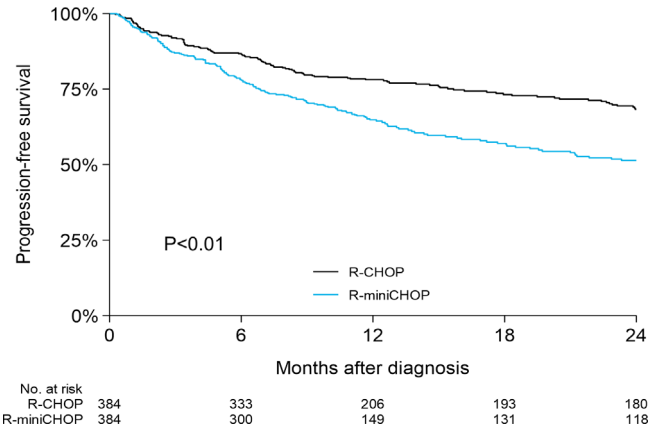

FIGURE 2 Progression-free survival (PFS) of patients with diffuse large B-cell lymphoma treated with R-miniCHOP and R-CHOP. Kaplan–Meier curves showing significant inferior 2-year PFS in patients treated with R-miniCHOP ($p < .01$). [Color figure can be viewed at wileyonlinelibrary.com]

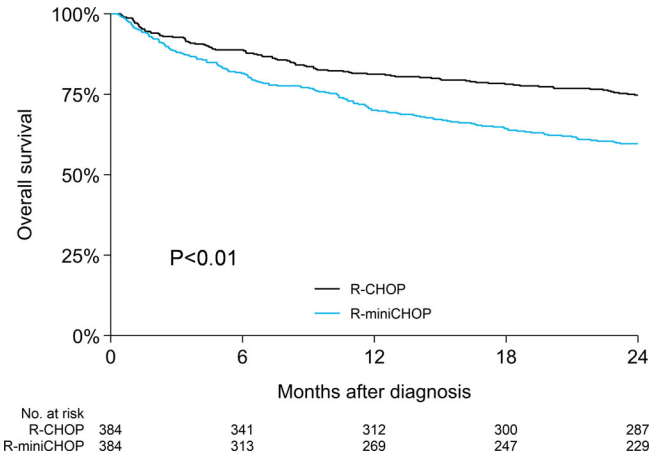

FIGURE 3 Overall survival (OS) of patients with diffuse large B-cell lymphoma treated with R-miniCHOP and R-CHOP. Kaplan–Meier curves showing a significant inferior 2-year OS in patients treated with R-miniCHOP ($p < .01$). [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

While R-CHOP remains the treatment of choice in fit patients with a newly diagnosed DLBCL, multiple alternative treatment regimens have been employed in unfit and frail patients. For frail elderly patients, options include rituximab, cyclophosphamide, vincristine and prednisone (R-COP), R-miniCHOP, rituximab, gemcitabine and oxaliplatin (R-GemOx), and rituximab-bendamustine.[11–13] In the current study, an increased use of R-miniCHOP was observed from 2014 onward following the landmark study by Peyrade et al.[3] Similar to the latter study, patients treated with R-miniCHOP in the general population had a median age >80 years and would be considered frail.[14]

The 2-year OS of elderly DLBCL patients treated with R-CHOP of 75% in this study was only slightly lower compared to 78% in a population-based DLBCL cohort.[2] In this study, the 2-year PFS estimate of 51% for patients treated with R-miniCHOP is in the range of reported outcomes of frail patients >80 years treated in clinical trials ranging from 47% to 57%.[3,6,15] The OS of patients treated with R-miniCHOP is in line with the reported outcome of the clinical trials with 2-year OS ranging from 59 to 68%.[3,6,7] The difference in OS between patients treated with R-miniCHOP and patients treated with R-CHOP was 15% in the current study. The same pattern was observed for RS and therefore, an inferior survival estimate cannot be attributed to comorbidities alone. The negative effect on OS for R-miniCHOP seems to contradict the observations from the UK population-based study who reported similar outcome for patients treated with R-CHOP and R-miniCHOP.[16] However, in the latter

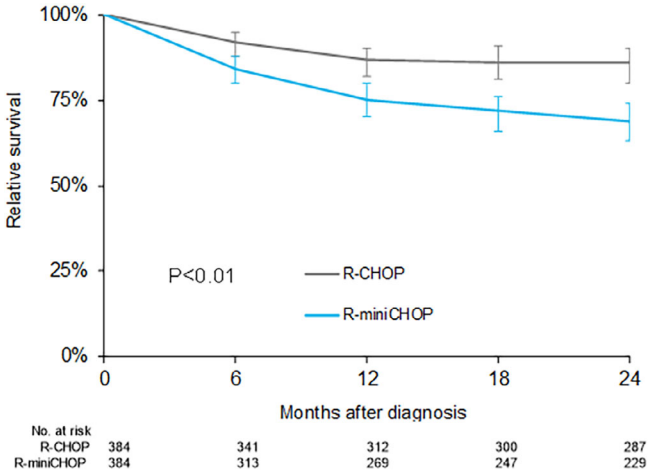

FIGURE 4 Relative survival (RS) of patients with diffuse large B-cell lymphoma treated with R-miniCHOP and R-CHOP. Kaplan–Meier curves showing a significant difference in 2-year RS in patients treated with R-miniCHOP ($p < .01$). [Color figure can be viewed at wileyonlinelibrary.com]

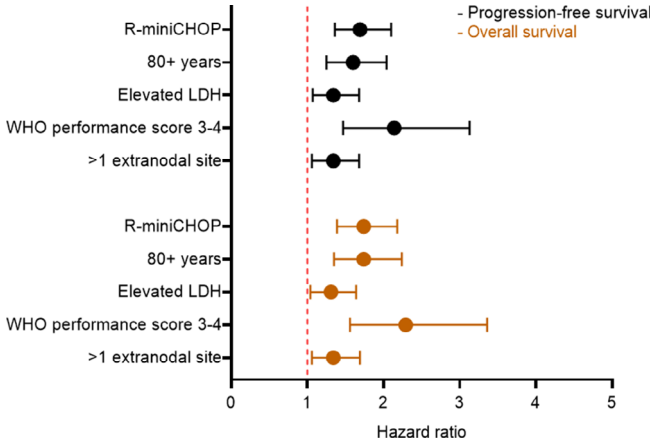

FIGURE 5 Results of the multivariable Cox regression analysis on progression-free survival and overall survival for patients with diffuse large B-cell lymphoma treated with R-miniCHOP versus R-CHOP. [Color figure can be viewed at wileyonlinelibrary.com]

study, no matching was performed on the patient- and treatment characteristics, for example, IPI-score and treatment regimen, thus hindering a comparison of the treatments, as patient groups were not balanced.

While R-miniCHOP is an effective treatment for the majority of unfit elderly patients at a substantially lower doses of doxorubicin and cyclophosphamide, there is a significant proportion of patients failing therapy. Several strategies could improve outcome. To select patients most suitable for R-miniCHOP, comprehensive geriatric assessment (CGA) tools might help to discriminate fit from unfit and frail patients. Recently, data were published by the Fondazione Italiana Linfomi (FIL) on the prognostic value of the elderly prognostic index (EPI), which combines results of the simplified CGA (sCGA), age (<and ≥80 years), ADL, IADL scores and anemia.[14] While the EPI is prognostic, no prospective trials have used it for patient selection or treatment allocation.

A second strategy to improve outcome could be pharmacokinetic (PK) monitoring and subsequent optimal dosing of CHOP chemotherapy. Currently dosing of R-CHOP is based on the body surface area (BSA). While in children significant differences have been observed for cyclophosphamide exposure during treatment,[17] little is known about the intra- and individual exposure to doxorubicin and cyclophosphamide in elderly patients. Altered body composition, renal insufficiency, decrease in liver function, and polypharmacy could all contribute to increased exposure to chemotherapy.[18] Observational PK monitoring studies have been performed in elderly patients treated with doxorubicin and cyclophosphamide, showing a decreased clearance compared to younger patients, but no interventional trials have been performed based on PK monitoring.[19–21]

Finally, incorporation of novel drugs to R-miniCHOP might improve outcome, but should be evaluated for additional toxicity. In patients treated with R-CHOP, the addition of polatuzumab vedotin improved PFS, but not OS.[22] Data of the randomized trial (NCT04332822) comparing R-miniCHOP alone versus R-miniCHP with polatuzumab in elderly and frail patients have not been published. While addition of ibrutinib to patients treated with R-CHOP did not improve outcome,[23] at the expense of additional toxicity, the phase 2 study combining R-miniCHOP with ibrutinib did improve survival compared to historical data.[7] Data with bispecific monoclonal antibodies are anticipated. In patients treated with R-CHOP and epcoritamab, the safety profile is manageable.[24] Mosunetuzumab has shown promising results with tolerable toxicity in unfit DLBCL patients as monotherapy.[25]

The main strength of this study was the use of a nationwide population-based cancer registry. This enabled us to identify all DLBCL patients who received R-miniCHOP in the Dutch population. Given the retrospective nature of our study, the reason for receiving R-miniCHOP is unknown. To reduce indication bias, propensity-score matching was performed. Limitations of our study mainly pertain to the lack of detailed information on comorbidities and COD, and performance score in 38% of the patients. Due to lacking information on COD and comorbidities in the NCR, RS, which is considered the gold-standard for performing a cause-specific survival analysis, was used to estimate DSS. Despite these limitations, this population-based cohort gives insight into the outcome of patient groups usually not eligible for clinical trials.

In conclusion, R-miniCHOP is an effective treatment for the majority of elderly patients. Although survival is inferior compared to R-CHOP, the usage of R-miniCHOP as initial treatment is increasing. Therefore, fitness needs to be carefully weighed in treatment selection.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest with regard to content of this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available via The Netherlands Comprehensive Cancer Organisation. These data are not publicly available, and restrictions apply to the availability of the data used for the current study. However, these data are available upon reasonable request and with permission of the Netherlands Comprehensive Cancer Organisation.

PATIENT CONSENT STATEMENT

Obtaining individual informed consent is not required for this type of observational studies containing no directly identifiable data.

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REFERENCES

1. Smith A, Crouch S, Lax S, et al. Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological malignancy research network. *Br J Cancer*. 2015;112(9):1575-1584.
2. Brink M, Kahle XU, Vermaat JSP, et al. Impact of rituximab biosimilars on overall survival in diffuse large B-cell lymphoma: a Dutch population-based study. *Blood Adv*. 2021;5(15):2958-2964.
3. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2011;12(5):460-468.
4. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26:v116-v125.
5. Zelenetz AD, Gordon LI, Wierda WG, et al. Diffuse large B-cell lymphoma version 1.2016. *J Natl Compr Canc Netw*. 2016;14(2):196-231.
6. Peyrade F, Bologna S, Delwail V, et al. Combination of ofatumumab and reduced-dose CHOP for diffuse large B-cell lymphomas in patients aged 80 years or older: an open-label, multicentre, single-arm, phase 2 trial from the LYSA group. *Lancet Haematol*. 2017;4(1):e46-e55.
7. Verner E, Johnston A, Pati N, et al. Efficacy of ibrutinib, rituximab and mini-CHOP in very elderly patients with newly diagnosed diffuse large B cell lymphoma: primary analysis of the Australasian Leukaemia; lymphoma group NHL29 study. *Blood*. 2021;138(suppl 1):304.
8. Schouten LJ, HÖPpener P, Van Den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol*. 1993;22(3):369-376.
9. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res*. 2011;46(3):399-424.
10. Ederer F, Heise H. *Instructions to IBM 650 programmers in processing survival computations. Methodological note No. 10. End results evaluation section*. National Cancer Institute; 1959.
11. Laribi K, Denizon N, Bolle D, et al. R-CVP regimen is active in frail elderly patients aged 80 or over with diffuse large B cell lymphoma. *Ann Hematol*. 2016;95(10):1705-1714.
12. Shen Q-D, Zhu H-Y, Wang L, et al. Gemcitabine-oxaliplatin plus rituximab (R-GemOx) as first-line treatment in elderly patients with diffuse large B-cell lymphoma: a single-arm, open-label, phase 2 trial. *Lancet Haematol*. 2018;5(6):e261-e269.
13. Storti S, Spina M, Pesce EA, et al. Rituximab plus bendamustine as front-line treatment in frail elderly (>70 years) patients with diffuse large B-cell non-Hodgkin lymphoma: a phase II multicenter study of the Fondazione Italiana Linfomi. *Haematologica*. 2018;103(8):1345-1350.
14. Merli F, Luminari S, Tucci A, et al. Simplified geriatric assessment in older patients with diffuse large B-cell lymphoma: the prospective elderly project of the Fondazione Italiana Linfomi. *J Clin Oncol*. 2021;39(11):1214-1222.
15. Oberic L, Peyrade F, Puyade M, et al. Subcutaneous rituximab-MiniCHOP compared with subcutaneous rituximab-MiniCHOP plus lenalidomide in diffuse large B-cell lymphoma for patients age 80 years or older. *J Clin Oncol*. 2021;39(11):1203-1213.
16. Hounsome L, Eyre TA, Ireland R, et al. Diffuse large B cell lymphoma (DLBCL) in patients older than 65 years: analysis of 3 year real world data of practice patterns and outcomes in England. *Br J Cancer*. 2022;126(1):134-143.
17. Veal GJ, Cole M, Chinnaswamy G, et al. Cyclophosphamide pharmacokinetics and pharmacogenetics in children with B-cell non-Hodgkin's lymphoma. *Eur J Cancer*. 2016;55:56-64.
18. Hughes VA, Frontera WR, Roubenoff R, Evans WJ, Singh MA. Longitudinal changes in body composition in older men and women: role of body weight change and physical activity. *Am J Clin Nutr*. 2002;76(2):473-481.
19. Baudry E, Huguet S, Couderc AL, et al. Cyclophosphamide dose adjustment based on body weight and albuminemia in elderly patients treated with R-mini-CHOP. *Cancer Chemother Pharmacol*. 2019;83(4):775-785.
20. Nakagawa J, Takahata T, Hyodo R, et al. Evaluation for pharmacokinetic exposure of cytotoxic anticancer drugs in elderly patients receiving (R-)CHOP therapy. *Sci Rep*. 2021;11(1):785.
21. Joerger M, Huitema ADR, Richel DJ, et al. Population pharmacokinetics and pharmacodynamics of doxorubicin and cyclophosphamide in breast cancer patients. *Clin Pharmacokinet*. 2007;46(12):1051-1068.
22. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab Vedotin in previously untreated diffuse large B-cell lymphoma. *New Eng J Med*. 2021;386(4):351-363.
23. Younes A, Sehn LH, Johnson P, et al. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non–germinal center B-cell diffuse large B-cell lymphoma. *J Clin Oncol*. 2019;37(15):1285-1295.
24. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *Lancet*. 2021;398(10306):1157-1169.
25. Olszewski AJ, Avigdor A, Babu S, et al. Single-agent Mosunetuzumab is a promising safe and efficacious chemotherapy-free regimen for elderly/unfit patients with previously untreated diffuse large B-cell lymphoma. *Blood*. 2020;136(supp 1):43-45.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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