Annals of Hematology (2019) 98:2729–2737
https://doi.org/10.1007/s00277-019-03819-3

ORIGINAL ARTICLE

Is bendamustine-rituximab a reasonable treatment in selected older patients with diffuse large B cell lymphoma? Results from a multicentre, retrospective study

Vanja Zeremski[1,2] · Kathleen Jentsch-Ullrich[3] · Christoph Kahl[4] · Martin Mohren[5] · Judith Eberhardt[1,2] · Thomas Fischer[1,2] · Enrico Schalk[1,2]

Received: 12 June 2019 / Accepted: 8 October 2019 / Published online: 8 November 2019

Abstract

Despite bendamustine-rituximab (BR) showed disappointing efficacy in diffuse large B cell lymphoma (DLBCL), it is still occasionally used as first-line treatment in older DLBCL patients instead of recommended R-CHOP. This multicentre, retrospective study was aimed to clarify circumstances in which BR may be justified in this setting. Patients ≥ 65 years with ECOG performance status (PS) ≥ 2 or ≥ 75 years regardless of PS were included. A total of 140 patients were analysed (BR, 68; R-CHOP, 72). BR patients were older ($p < 0.001$) and were diagnosed more often with high-risk disease ($p = 0.03$); no difference regarding comorbidities or PS was seen. Compared with R-CHOP, BR was associated with marked inferior overall survival (OS) (16.3 vs. 75.4 months; $p = 0.006$) and progression-free survival (PFS) (11.0 vs. 62.3 months; $p < 0.001$). In multivariate analysis, only high age-adjusted Charlson Comorbidity Index (aaCCI) was associated with inferior PFS in R-CHOP patients (hazard ratio 2.67; $p = 0.012$). Comparing the subgroup of BR and R-CHOP patients with high aaCCI, there was no difference in OS ($p = 0.73$) or PFS ($p = 0.75$). Due to the observed non-superiority of R-CHOP in older DLBCL patients with comorbidities, we propose that this subgroup may be treated alternatively with BR, whereas all other older patients are clearly R-CHOP candidates.

Keywords Diffuse large B cell lymphoma · Bendamustine · R-CHOP · Older patients · Comorbidities

Introduction

Diffuse large B cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma (NHL) occurring commonly in older patients, with a median age of 70 years at diagnosis [1, 2]. The former definition of 'older NHL patients' as patients older than 60 years [3] seems to be abandoned. The age of 75 years was suggested as a new cut-off for 'older patients', due to higher prevalence of comorbidities and age-related physiological changes in this age group [4, 5]. However, when defining an older patient, other factors in addition to chronological age must be considered, i.e. functional status and comorbidities.

Standard treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) is advised irrespective of patient's age [6–8], despite higher toxicity rates reported in older patients [9, 10]. In order to minimize toxicity and improve quality of life, R-CHOP was often challenged, and diverse reduced-intensity dose regimens with/without anthracyclines were tested [11–14].

Bendamustine is a cytotoxic alkylating agent that is worldwide approved for the treatment of chronic lymphocytic leukaemia and other indolent NHL. In combination with rituximab (BR), it was shown not only to be efficient but also well tolerated in indolent NHL [15, 16]. Consequently, BR was tested in DLBCL patients, initially in relapse/refractory settings and then also as first-line treatment [17–19]. The

✉ Vanja Zeremski
vanja.zeremski@med.ovgu.de

1 Department of Haematology and Oncology, Otto-von-Guericke University Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany

2 Health Campus Immunology, Infectiology and Inflammation (GC-I3), Medical Centre, Otto-von-Guericke University, Magdeburg, Germany

3 Private Practice for Haematology and Oncology, Magdeburg, Germany

4 Department of Haematology, Oncology and Palliative Care, Klinikum Magdeburg, Magdeburg, Germany

5 Department of Hematology and Oncology, Johanniter Krankenhaus, Stendal, Germany

Table 1 Patients' baseline characteristics

Variables	Total (n = 140)	BR (n = 68)	R-CHOP (n = 72)	p value
Age				
Median (range), years	79 (65–93)	80 (68–91)	77 (65–93)	$p < 0.001$
Age				
≥ 80 years (n)	56 (40.0%)	36 (52.9%)	20 (27.8%)	$p < 0.001$
Sex (n)				
Male	69/140 (49.3%)	35/68 (51.5%)	34/72 (48.6%)	$p = 0.73$
ECOG performance status (n)				
0–1	84/132 (63.6%)	41/65 (63.1%)	43/67 (64.2%)	$p = 1.0$
2–4	48/132 (36.4%)	24/65 (36.9%)	24/67 (35.8%)	
n/a	8	3	5	
aaCCI score (n)				
Low (2–3)	30/140 (21.4%)	12/68 (17.6%)	18/72 (25.0%)	$p = 0.36$
Intermediate (4–5)	78/140 (55.7%)	42/68 (61.8%)	36/72 (50.0%)	
High (≥ 6)	32/140 (22.9%)	14/68 (20.6%)	18/72 (25.0%)	
LVEF ≤ 50% (n)				
Yes	21/96 (21.9%)	14/48 (29.2%)	7/48 (14.6%)	$p = 0.14$
n/a	44	20	24	
Ann Arbor stage (n)				
Limited (I–II)	53/140 (37.9%)	20/68 (29.4%)	33/72 (45.8%)	$p = 0.06$
Advanced (III–IV)	87/140 (62.1%)	48/68 (70.6%)	39/72 (54.2%)	
Extranodal involvement (n)				
Yes	105/140 (75.0%)	55/68 (80.9%)	50/72 (69.4%)	$p = 0.17$
Bulky disease (n)				
Yes	39/136 (28.7%)	21/67 (31.3%)	18/69 (26.1%)	$p = 0.57$
n/a	4	1	3	
aaIPI (n)				
Low (0–1)	51/127 (40.2%)	20/60 (30.0%)	33/67 (49.3%)	$p = 0.03$
High (2–3)	76/127 (59.8%)	42/60 (70.0%)	34/67 (50.7%)	
n/a	13	8	5	

BR bendamustine, rituximab; *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; *ECOG*: Eastern Cooperative Oncology Group; *n/a* not available; *aaCCI* age-adjusted Charlson Comorbidity Index; *LVEF* left ventricular ejection fraction; *aaIPI* age-adjusted international prognostic score

outcome was rather disappointing. Nevertheless, BR is still occasionally used as first-line treatment in DLBCL [20–22], leaving the question whether this is justified as an alternative to R-CHOP and what are the appropriate candidates for this treatment approach. To answer that, we have retrospectively analysed clinical characteristics and outcomes of older DLBCL patients treated with BR in first-line and compared them to other older DLBCL patients treated with R-CHOP regimen.

Materials and Methods

Study design

This retrospective study was conducted at four institutions in Germany on older consecutive patients with de novo DLBCL diagnosed from February 2008 until September 2017, with last follow-up as of January 2019. Of note, older patients were defined as those ≥ 65 years with Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2 or those ≥75 years regardless of PS [4, 5, 14]. Only patients that received BR or R-CHOP were included in this analysis. All other patients treated with best supportive care, radiation or surgery treatment only as well as those treated with alternative regimen (i.e. R-CVP, R-GCVP) were not included in this study. Patients with relapsed/refractory DLBCL, secondary DLBCL and primary central nervous system lymphoma were excluded. Data regarding patients' characteristics, diagnosis, therapy and outcome were obtained reviewing patients' medical history. Given the advanced age in this analysed population, we used the age-adjusted Charlson Comorbidity Index (aaCCI) in order to assess comorbidities [23]. Other than in the original aaCCI, no point was assigned for the presence of

DLBCL. Due to retrospective nature of the study, comprehensive geriatric assessment was not possible. The age-adjusted International Prognostic Index (aaIPI) was applied as a prognostic score [3]. This study was approved by the institutional Ethical Committees. Written informed consent was not taken due to this retrospective, non-interventional study. All procedures were performed in accordance with the general ethical principles outlined in the Declaration of Helsinki [24].

Treatment

Patients were assigned to therapeutic strategy according to physicians' discretions. BR regimen was administered at the following dose: bendamustine 90 mg/m^2 on days 1 and 2 combined with 375 mg/m^2 rituximab on day 1 every 4 weeks, for up to 6 cycles [15]. In case of dose reduction, bendamustine was applied at dose of 70 mg/m^2. Alternatively, patients received R-CHOP at standard dose or reduced dose, for up to 8 cycles. Dose reduction included the so-called R-miniCHOP [12] as well as each single or combined dose reduction of cyclophosphamide, doxorubicin or vincristine up to 50% at any time of treatment. Patients with bulky disease, defined as tumour mass > 7.5 cm, and/or advanced disease received consolidation radiotherapy when possible. In cases of testicular or craniofacial involvement of lymphoma, prophylactic intrathecal chemotherapy with methotrexate was applied. Majority of the patients received a prephase treatment consisting of prednisolone with or without vincristine [5].

Outcome

Treatment response was evaluated according to international workshop criteria for NHL [25]. Overall response (ORR) rate was defined as the sum of complete and partial remissions. Overall survival (OS) and progression-free survival (PFS) were defined according to published recommendations [26].

Statistical analysis

Comparison of categorical variables was done using Pearson's chi-square test or Fisher's exact test, when possible. Comparison of continuous variables was done using Mann-Whitney *U* test. OS and PFS were estimated by the Kaplan-Meier method and the comparison between groups was done using log-rank test. The median follow-up time was derived from OS using 'reverse' Kaplan-Meier estimates. In order to identify a subgroup of patients that do not benefit, regarding OS and PFS, from R-CHOP treatment, we performed unadjusted univariate and multivariate analysis in these patients using a Cox's proportional hazards model. Two-tailed *p* values < 0.05 were considered statistically significant. Statistical analysis was carried out using SPSS, version 24.

Results

Patients' characteristics

Altogether, 140 older patients were identified that met above-stated inclusion criteria. Median age at the diagnosis was 79 years (range 65–93). About one-third of the patients (36.4%) had poor PS (ECOG 2-4) and 33 patients (22.9%) had severe comorbidities, corresponding aaCCI ≥ 6. Sixty-eight patients (48.6%) received BR and 72 patients (51.4%) received R-CHOP. Patients that received BR regimen were older ($p < 0.001$) and had more often high-risk disease ($p = 0.03$). No difference regarding other clinical parameters was observed. Patients' baseline characteristics are summarized in Table 1.

Treatment and Outcome

Treatment pattern and treatment response are shown in Table 2. Data regarding treatment response were missing in 29 patients (18 with BR and 11 with R-CHOP), due to loss to follow-up (8 patients) or death prior to response evaluation (21 patients).

Overall, median follow-up was 49.9 months (95% confidence interval [95% CI] 31.4–68.4). Seventy-three deaths were documented during treatment and follow-up, of which 42 (62.8%) were in the BR group and 31 (43.1%) in the R-CHOP group. Median OS and PFS in the entire study

Table 2 Treatment pattern and treatment response

	BR ($n = 68$)	R-CHOP ($n = 72$)	*p* value
Number of cycles (*n*)			
Median (range)	6 (1–6)	6 (1–8)	
≤ 3	18/68 (26.5%)	23/72 (31.9%)	
6	43/68 (58.1%)	36/72 (50.0%)	
Dose reduction (*n*)			
Initially	13/68 (19.1%)	23/72 (31.9%)	$p = 0.12$
Intrathecal therapy (*n*)			
Yes	3/68 (4.4%)	8/72 (11.1%)	$p = 0.21$
Radiotherapy (*n*)			
Yes	8/68 (11.8%)	23/66 (34.8%)	$p = 0.002$
n/a	0	6	
Treatment response (*n*)			
ORR	42/50 (84.0%)	57/61 (93.4%)	$p = 0.13$
CR	28/50 (56.0%)	47/61 (77.0%)	
PR	14/50 (28.0%)	10/61 (16.4%)	
n/a	18	11	
Progression/relapse	23/48 (47.9%)	10/53 (18.9%)	$p = 0.003$

BR bendamustine, rituximab; *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; *ORR* overall response rate; *CR* complete remission; *PR* partial remission; *n/a* not available

population were 30.4 months (95% CI 0–65.6) and 23.3 months (95% CI 11.3–35.3), respectively. Patients that received BR had a significantly inferior outcome than patients with R-CHOP regimen: median OS was 16.3 months (95% CI 10.6–22.0) and 75.4 months (95% CI 49.0–101.8) ($p = 0.006$), respectively. A significant difference regarding PFS was also observed comparing BR and R-CHOP treatment (11.0 months [95% CI 5.0–17.0] vs. 62.3 months [95% CI 50.2–74.4]; $p < 0.001$), respectively. OS and PFS according to treatment are shown in Fig. 1.

Univariate and multivariate analysis of risk factors for OS and PFS among patients treated with R-CHOP are shown in Table 3. Only high (≥ 6) aaCCI was shown to be an independent, negative predictive factor for PFS (hazard ratio [HR] 2.67 [95% CI 1.24–5.72]; $p = 0.012$).

Based on that, we identified 32 patients (22.9%) in the entire population with a high aaCCI, and performed a subgroup analysis on these patients; 14 of them were treated with BR and 18 with R-CHOP regimen. Within this subgroup, there was no difference between the BR and R-CHOP group

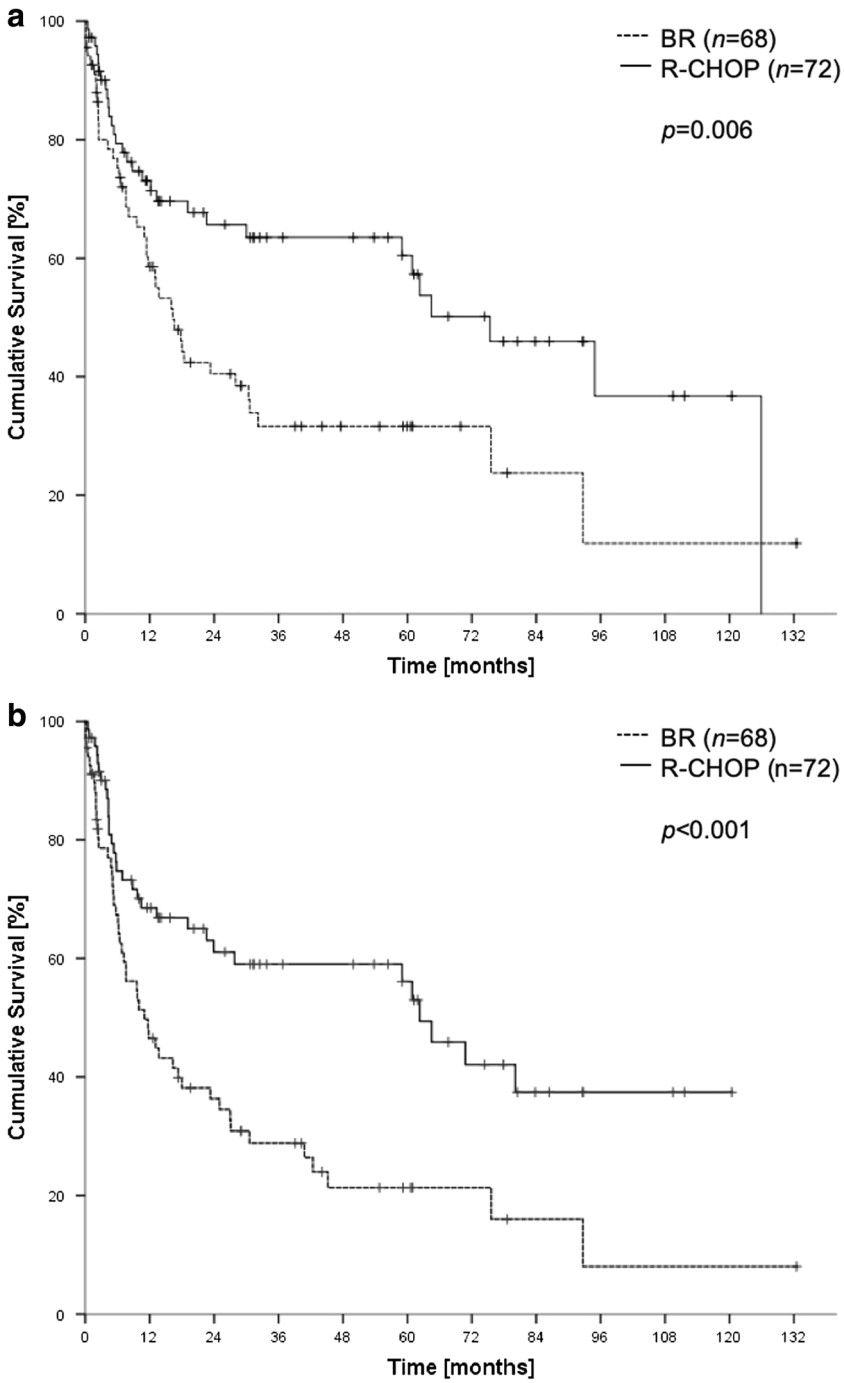

Fig. 1 **a** Overall survival according to treatment. **b** Progression-free survival according to treatment

Table 3 Univariate and multivariate analysis of OS and PFS in R-CHOP patients

Variable	Univariate analysis			Multivariate analysis		
OS	HR	95% CI	*p* value	HR	95% CI	*p* value
Age ≥ 80 years	1.37	0.62–3.02	0.43	1.24	0.50–3.04	0.64
Sex (male)	1.34	0.64–2.80	0.43	1.41	0.63–3.16	0.40
ECOG 2–4	1.39	0.62–3.16	0.42	0.95	0.32–2.84	0.93
High aaCCI (≥6)	2.27	1.07–4.80	0.03	2.07	0.91–4.70	0.08
Advanced stage (III–IV)	1.42	0.67–3.02	0.36	0.99	0.34–2.88	0.99
Bulky disease	0.82	0.33–2.03	0.67	0.76	0.33–2.26	0.86
Extranodal manifestation	0.91	0.42–1.96	0.81	0.98	0.37–2.62	0.98
aaIPI high (2–3)	1.32	0.61–2.90	0.48	1.50	0.65–3.47	0.34
PFS						
Age ≥ 80 years	1.34	0.64–2.85	0.44	1.25	0.52–3.0	0.62
Sex (male)	1.12	0.58–-2.35	0.66	1.02	0.45–2.29	0.96
ECOG 2–4	1.60	0.75–3.42	0.22	0.89	0.30–2.67	0.84
High aaCCI (≥6)	2.79	1.36–5.69	0.005	2.67	1.24–5.72	0.012
Advanced stage (III–IV)	1.38	0.67–2.83	0.37	0.79	0.23–2.74	0.72
Bulky disease	0.67	0.27–1.63	0.38	1.69	0.77–3.71	0.19
Extranodal manifestation	1.02	0.48–2.16	0.96	1.12	0.45–2.80	0.80
aaIPI high (2–3)	1.39	0.66–2.92	0.39	1.68	0.76–3.69	0.20

OS overall survival; *PFS* progression-free survival; *HR* hazard ratio; *CI* confidence interval; *ECOG* Eastern Cooperative Oncology Group; *n/a* not available; *aaCCI* age-adjusted Charlson Comorbidity Index; *aaIPI* age-adjusted International Prognostic Score

regarding OS (16.6 months [95% CI 0–39.4] vs. 22.6 months [95% CI 3.15–42.5]; $p = 0.73$) and PFS (9.6 months [95% CI 2.5–16.7] vs. 10.4 months [95% CI 0.2–20.6]; $p = 0.75$) as shown in Fig 2. ORR was also comparable (77.8% vs. 83.3%; $p = 1.0$).

When comparing only patients aged ≥ 80 years regardless of PS ($n = 56$), treatment with R-CHOP showed benefit compared with treatment with BR, even when statistical significance was not reached (PFS was 59.0 [95% CI 13.7–104.3 months] vs.11.0 months [95% CI 5.0–17.9], respectively; $p = 0.06$).

Discussion

The management of older patients with DLBCL poses a great challenge. They present with similar clinical characteristics as their younger counterparts [17, 27, 28]; however, difficulties are seen in age-related comorbidities, polypharmacy, heterogenous functional status and lack of social support in older patients. Given this context, physicians are often concerned regarding patients' eligibility for the standard R-CHOP treatment. Additionally, some of the older patients refuse therapy advised by their oncologists. As a result, one-third of DLBCL patients > 75 years receive no treatment at all in routine clinical care [9, 27, 29].

Despite the general recommendation to apply R-CHOP as first-line treatment [6–8], only about half of older DLBCL patients (50–60%) are treated in this manner [29, 30]. The use of alternative regimens seems to be increasing [13, 14, 29].

BR is regarded to be very effective in indolent NHL [16, 31]; however, its efficacy in DLBCL seems to be rather disappointing. In two small phase II studies (13 and 24 patients, respectively) on older, de novo DLBCL patients, bendamustine was applied at a dose of 120 mg/m^2 in combination with rituximab every 21 days. The reported median PFS in both studies was about 6 months [17, 18]. One of these studies included only patients with advanced disease [18] and the other one only patients ≥ 80 years [17]. Storti et al. conducted recently a trial with BR in older (> 70 years) and frail DLBCL patients ($n = 45$). Bendamustine was given at lower dose (90 mg/m^2) every 4 weeks up to 6 cycles. This less intense approach was very well tolerated with only 15% reported severe toxicities. The median PFS was 10 months [19].

To the best of our knowledge, our retrospective, multicentre study analysed the largest population of de novo DLBCL patients treated with BR. Clinical characteristics of our 68 BR patients were comparable to those in the trial from Storti et al., not taken into account comprehensive geriatric assessment, which was not available in our analysis due to its retrospective nature. Treatment pattern of BR, dose and schedule, was also the same, and more importantly, findings regarding PFS (median PFS 11.0 months) were comparable with those from Storti et al. [19]. This implies that data from this controlled clinical trial indeed reflect real-world patients and outcomes.

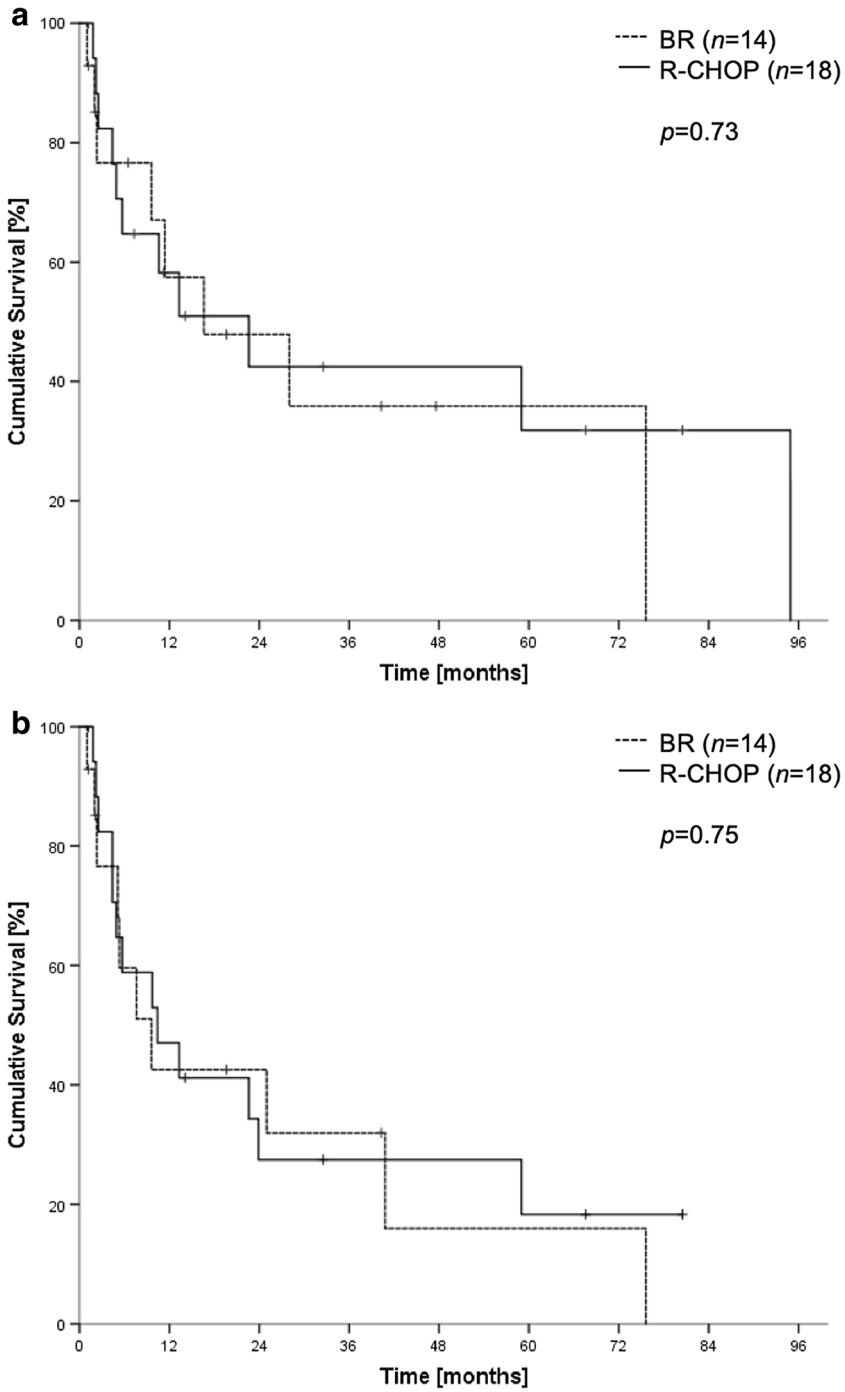

Fig. 2 **a** Subgroup analysis of overall survival in patients with high (≥ 6) age-adjusted Charlson Comorbidity Index according to treatment. **b** Subgroup analysis of progression-free survival in patients with high (≥ 6) age-adjusted Charlson Comorbidity Index according to treatment

Of note, our patients treated with BR had significantly inferior PFS compared with those treated with R-CHOP regimen (about 4 years; $p < 0.001$). Despite that BR initially showed high efficacy (ORR 84.0%), half of these patients (47.9%) experienced relapse/progression compared with only about 20% treated with R-CHOP ($p = 0.003$). These findings are consistent with the recently published data [21]; however, our data have to be interpreted with caution due to the low number of response data. About one-third of R-CHOP patients proceeded to consolidation radiotherapy compared with only 11% BR patients ($p = 0.002$). The outcome of BR with or without radiotherapy was inferior compared with R-CHOP (data not shown).

Due to retrospective character of the study, data regarding choice of treatment regimen (BR vs. R-CHOP) are not known, leaving thereby a potential selection bias. The comparison of these patient groups showed that our R-CHOP patients were significantly younger and had less frequently high-risk disease compared with BR patients. Yet none of these parameters was shown to have an impact on survival in our study. Regarding

PS and comorbidities, factors that are commonly referred as those that influence treatment choice, we observed no difference between R-CHOP and BR patients, implying that treatment decision was often subjective and not based on a rational basis. Defining patients as not R-CHOP candidates should be made with caution, because alternative regimens can obviously result in undertreatment.

The IPI was known to be a valuable prognostic factor in DLBCL. Interestingly, neither aaIPI nor factors included in the original IPI were shown to be predictive for OS or PFS in our analysis. This might reflect the fact that our patient population is not representative (i.e. small sample size). Another possible explanation is that in older DLBCL patients, the negative prognostic impact of high comorbidity burden overbalances all other prognostic factors. This is supported by the fact that other authors also failed to prove the value of these prognostic factors in older DLBCL patients [6, 21].

Comorbidities are known to be an independent prognostic factor for survival in DLBCL patients [1, 6]. To evaluate these, we used in our study the aaCCI, a comorbidity score that takes into account not only number of comorbidities but also patient's age (for each decade above the fourth additional point is assigned). Its independent predictive value regarding PFS could be confirmed in our cohort treated with R-CHOP (HR 2.67; $p = 0.012$). When analysing survival in the subgroup of patients that were not only old but also comorbid (with high aaCCI ≥6), no difference in terms of survival was observed irrespective of the applied treatment (PFS in BR and R-CHOP was 9.6 months and 10.4 months, respectively; $p = 0.73$). That implies that old and comorbid patients, who are not seen as candidates for a curative approach, may be treated with BR in the first-line setting. It seems that they do not benefit from the treatment intensification with R-CHOP. Given the lower toxicity profile [16, 21, 31], compared with other alternative regimens (i.e. R-CVP), BR could be preferred in the palliative constellation of old and comorbid DLBCL patients.

All other patients, including very old (≥ 80 years) but fit ones, are R-CHOP candidates. A subgroup analysis of our patients ≥80 years, irrespective of PS, showed that they do benefit from R-CHOP compared with BR treatment (PFS was 59.0 months vs. 11.0 months; $p = 0.06$). However, the question of appropriate R-CHOP dose remains unclear. Due to higher toxicity reported in this patient population [9, 10], dose reduction seems to be meaningful. Particularly, when considering that moderate dose reduction is not supposed to negatively affect survival [6, 30]. Alternatively, R-miniCHOP [12] could be applied in very old patients due to apparently acceptable toxicity and superior efficacy compared with BR. In our population, we observed no difference in terms of survival regardless of applied dose (data not shown).

Well known, relevant limitations of our data are the retrospective character of this study with a potential selection bias, and low sample size in the subgroup analysis. However, prospective data, especially in the setting of multicentre, randomized controlled trials, in this patients' group are rare and not to be expected [32–34]. This is why such real-life data and retrospective studies help to better understand this patient population and to improve treatment.

The results of our retrospective study highlight that it is important to follow recommendations for curative treatment of older DLBCL patients with R-CHOP, irrespective of age, whenever possible. Treatment with alternative regimens seems to be futile. Only in the subgroup of old and comorbid patients, when a palliative approach is intended, BR could be applied given the potential lower-toxicity profile and comparable outcome to R-CHOP.

Conflict of interest The authors declare that they have no conflict of interest.

Funding information This research was supported by a grant from the German Research Foundation (DFG; SFB854).

Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

References

1. Saygin C, Jia X, Hill B, Dean R, Pohlman B, Smith MR, Jagadeesh D (2017) Impact of comorbidities on outcomes of elderly patients with diffuse large B-cell lymphoma. Am J Hematol 92:989–996. https://doi.org/10.1002/ajh.24819
2. Morrison VA, Shou Y, Bell JA, Hamilton L, Ogbonnaya A, Raju A, Hennenfent K, Eaddy M, Galaznik A (2019) Evaluation of treatment patterns and survival among patients with diffuse large B-cell lymphoma in the USA. Future Oncol 15:1021–1034. https://doi.org/10.2217/fon-2018-0788
3. The International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993) A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987–994
4. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW (2005) Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 55:231–240. https://doi.org/10.1016/j.critrevonc.2005.04.008
5. Pfreundschuh M (2010) How I treat elderly patients with diffuse large B-cell lymphoma. Blood 116:5103–5110. https://doi.org/10.1182/blood-2010-07-259333
6. Chihara D, Westin JR, Oki Y, Ahmed MA, Do B, Fayad LE, Hagemeister FB, Romaguera JE, Fanale MA, Lee HJ, Turturro F, Samaniego F, Neelapu SS, Rodriguez MA, Fowler NH, Wang M, Davis RE, Nastoupil LJ (2014) Management strategies and outcomes for very elderly patients with diffuse large B-cell lymphoma. Cancer 122:3145–3151. https://doi.org/10.1002/cncr.30173
7. Buske C, Hutchings M, Ladetto M, Goede V, Mey U, Soubeyran P, Spina M, Stauder R, Trneny M, Wedding U, Fields P, ESMO Lymphoma Consensus Conference Panel Members (2018) ESMO Consensus Conference on malignant lymphoma: general perspectives and recommendations for the clinical management of the

elderly patient with malignant lymphoma. Ann Oncol 29:544–562. https://doi.org/10.1093/annonc/mdx413
8. Kumar A, Fraz MA, Usman M, Malik SU, Ijaz A, Durer C, Durer S, Tariq MJ, Khan AY, Qureshi A, Faridi W, Nasar A, Anwer F (2018) Treating diffuse large B cell lymphoma in the very old or frail patients. Curr Treat Options in Oncol 19:50. https://doi.org/10.1007/s11864-018-0565-6
9. Boslooper K, Kibbelaar R, Storm H, Veeger NJ, Hovenga S, Woolthuis G, van Rees B, de Graaf E, van Roon E, Kluin-Nelemans HC, Joosten P, Hoogendoorn M (2014) Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone is beneficial but toxic in very elderly patients with diffuse large B-cell lymphoma: a population-based cohort study on treatment, toxicity and outcome. Leuk Lymphoma 55:526–532. https://doi.org/10.3109/10428194.2013.810737
10. Byun JM, Lee JO, Kang B, Kim JW, Kim SH, Kim JW, Kim YJ, Lee KW, Bang SM, Lee JS (2016) Diffuse large B-cell lymphoma in the elderly: real world outcomes of immunochemotherapy in Asian population. Clin Lymphoma Myeloma Leuk 16:503–510. https://doi.org/10.1016/j.clml.2016.06.003
11. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, Solal-Celigny P, Offner F, Walewski J, Raposo J, Jack A, Smith P (2005) CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 105:1417–1423. https://doi.org/10.1182/blood-2004-08-3175
12. Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S, Coiffier B, Haioun C, Bologna S, Fitoussi O, Lepeu G, Fruchart C, Bordessoule D, Blanc M, Delarue R, Janvier M, Salles B, André M, Fournier M, Gaulard P, Tilly H, Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators (2011) 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 12:460–468. https://doi.org/10.1016/S1470-2045(11)70069-9
13. Fields PA, Townsend W, Webb A, Counsell N, Pocock C, Smith P, Jack A, El-Mehidi N, Johnson PW, Radford J, Linch DC, Cunnningham D (2014) De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. J Clin Oncol 32:282–287. https://doi.org/10.1200/JCO.2013.49.7586
14. Shen QD, Zhu HY, Wang L, Fan L, Liang JH, Cao L, Wu W, Xia Y, Li JY, Xu W (2018) 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 5:e261–e269. https://doi.org/10.1016/S2352-3026(18)30054-1
15. Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, Josten KM, Dürk H, Rost A, Neise M, von Grünhagen U, Chow KU, Hansmann ML, Hoelzer D, Mitrou PS (2005) Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 23:3383–3389. https://doi.org/10.1200/JCO.2005.08.100
16. Flinn IW, van der Jagt R, Kahl BS, Wood P, Hawkins TE, Macdonald D, Hertzberg M, Kwan YL, Simpson D, Craig M, Kolibaba K, Issa S, Clementi R, Hallman DM, Munteanu M, Chen L, Burke JM (2014) Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 123:2944–2952. https://doi.org/10.1182/blood-2013-11-531327
17. Weidmann E, Neumann A, Fauth F, Atmaca A, Al-Batran SE, Pauligk C, Jäger E (2011) Phase II study of bendamustine in combination with rituximab as first-line treatment in patients 80 years or older with aggressive B-cell lymphomas. Ann Oncol 22:1839–1844. https://doi.org/10.1093/annonc/mdq671
18. Park SI, Grover NS, Olajide O, Asch AS, Wall JG, Richards KL, Sobol AL, Deal AM, Ivanova A, Foster MC, Muss HB, Shea TC (2016) A phase II trial of bendamustine in combination with rituximab in older patients with previously untreated diffuse large B-cell lymphoma. Br J Haematol 175:281–289. https://doi.org/10.1111/bjh.14232
19. Storti S, Spina M, Pesce EA, Salvi F, Merli M, Ruffini A, Cabras G, Chiappella A, Angelucci E, Fabbri A, Liberati AM, Tani M, Musuraca G, Molinari A, Petrilli MP, Palladino C, Ciancia R, Ferrario A, Gasbarrino C, Monaco F, Fraticelli V, De Vellis A, Merli F, Luminari S (2018) 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 103:1345–1350. https://doi.org/10.3324/haematol.2017.186569
20. Hammersen FJ, Sommer M, Gössel C, Teichgräber U, Hahnfeld S, Scholl S, Fricke HJ, Wedding U, Ekkehard E, Iver P, Merz H, Hochhaus A, La Roséee P (2013) Safety and efficacy of bendamustine in patients with aggressive non-Hodgkin lymphomas (NHL). Blood 122:4371
21. Cheng CL, Liu JH, Chou SC, Yao M, Tang JL, Tien HF (2018) Retrospective analysis of frontline treatment efficacy in elderly patients with diffuse large B-cell lymphoma. Eur J Haematol 101:28–37. https://doi.org/10.1111/ejh.13069
22. Hammersen FJ, Rüthrich MM, Wedding U, Sommer M, Hochhaus A, La Rosee P (2018) Comparison of R-miniCHOP with R-Bendamustine (R-B) in diffuse large B-cell Lymphoma (DLBCL) in elderly and comorbid patients. Oncol Res Treat 41(suppl 4):44 abstract P173
23. Charlson M, Szatrowski TP, Peterson J, Gold J (1994) Validation of a combined comorbidity index. J Clin Epidemiol 47:1245–1251
24. World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310:2191–2194. https://doi.org/10.1001/jama.2013.281053
25. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-López A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 17:1244–1253. https://doi.org/10.1200/JCO.1999.17.4.1244
26. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V, International Harmonization Project on Lymphoma (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579–586. https://doi.org/10.1016/j.hoc.2007.06.011
27. Hamlin PA, Satram-Hoang S, Reyes C, Hoang KQ, Guduru SR, Skettino S (2014) Treatment patterns and comparative effectiveness in elderly diffuse large B-cell lymphoma patients: a surveillance, epidemiology, and end results-medicare analysis. Oncologist 19:1249–1257. https://doi.org/10.1634/theoncologist.2014-0113
28. Diem S, Ess S, Cerny T, Früh M, Hitz F (2014) Diffuse large B-cell lymphoma in elderly patients: a retrospective analysis. Eur J Intern Med 25:577–582. https://doi.org/10.1016/j.ejim.2014.05.001
29. Tien YY, Link BK, Brooks JM, Wright K, Chrischilles E (2015) Treatment of diffuse large B-cell lymphoma in the elderly: regimens without anthracyclines are common and not futile. Leuk Lymphoma 56:65–71. https://doi.org/10.3109/10428194.2014.903589
30. Juul MB, Jensen PH, Engberg H, Wehberg S, Dessau-Arp A, Haziri D, Kristensen HB, Baech J, Schurmann L, Clausen MR, Valentin R, Knudsen LM, Munksgaard L, El-Galaly TC, Frederiksen H, Larsen TS (2018) Treatment strategies and outcomes in diffuse large B-cell

lymphoma among 1011 patients aged 75 years or older: A Danish population-based cohort study. Eur J Cancer 99:86–96. https://doi.org/10.1016/j.ejca.2018.05.006

31. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, Kofahl-Krause D, Heil G, Welslau M, Balser C, Kaiser U, Weidmann E, Dürk H, Ballo H, Stauch M, Roller F, Barth J, Hoelzer D, Hinke A, Brugger W, Study group indolent Lymphomas (StiL) (2013) Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, bendamustine, bendamustine, phase 3 non-inferiority trial. Lancet 381:1203–1210. https://doi.org/10.1016/S0140-6736(12)61763-2
32. Bellera C, Praud D, Petit-Monéger A, McKelvie-Sebileau P, Soubeyran P, Mathoulin-Pélissier S (2013) Barriers to inclusion of older adults in randomised controlled clinical trials on non-Hodgkin's lymphoma: a systematic review. Cancer Treat Rev 39:812–817. https://doi.org/10.1016/j.ctrv.2013.01.007
33. Hamaker ME, Stauder R, van Munster BC (2014) On-going clinical trials for elderly patients with a hematological malignancy: are we addressing the right end points? Ann Oncol 25:675–681. https://doi.org/10.1093/annonc/mdt592
34. ClinicalTrials.gov (2019) https://clinicaltrials.gov (accessed at 11/06/2019)