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Comprehensive Geriatric Assessment is useful in an elderly Australian population with Diffuse Large B-cell Lymphoma receiving Rituximab-chemotherapy combinations.

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Summary:
Elderly patients may be heterogeneous in their abilities to tolerate immunochemotherapy-associated toxicities. We describe the morbidity of rituximab-chemotherapy combinations among 205 newly-diagnosed diffuse large B-cell lymphoma (DLBCL) patients aged ≥60 years from 3 tertiary hospitals between 2009 and 2016, and explore the utility of retrospectively-assigned baseline Comprehensive Geriatric Assessment (CGA) in predicting these toxicities. Seventy-three percent (146/201) experienced grade ≥3 toxicities, 81% (163/201) needed admission, 52% (107/205) had ≥2 unplanned admissions, 82/201 (41%) required dose reductions (DR) subsequent to Cycle 1, 39/166(23%) had chemotherapy delays and 26/198(13%) ceased therapy early. CGA was associated with pre-emptive baseline DR and perhaps because of this, did not predict grade ≥3 toxicities, ≥2 unplanned admissions or subsequent DR. Three-year overall survival (OS) of CGA-fit, CGA-unfit and CGA-frail patients was 82%, 60% and 53%, respectively. Three-year progression-free survival (PFS) of CGA-fit, CGA-unfit and CGA-frail patients was 66%, 58% and 46%, respectively. OS of CGA-fit patients was not statistically different from CGA-unfit patients, but was superior to CGA-frail patients (Hazard ratio 2.892, 95% confidence interval 1.275-6.559, p=0.011). PFS differences were not statistically significant. Baseline DR and early therapy cessation were associated with inferior OS and PFS independent of CGA. Prospective studies are needed to confirm if CGA-adapted treatment strategies minimize morbidity and improves survival.

Keywords:
Geriatric assessment, elderly, DLBCL, lymphoma, morbidity

Introduction

Rituximab-chemotherapy combinations for diffuse large B cell lymphoma (DLBCL) is well tolerated in clinical trial populations of elderly patients (Coiffier et al., 2002; Habermann et al., 2006; Peyrade et al., 2011; Pfreundschuh et al., 2006), however these data may not reflect real-world practice, and usual methods of grading toxicity may underestimate the clinical morbidity experienced by these patients and clinical decision-making in response to the toxicity. Achieving a balance between overtreating frail older cohorts and undertreating fit elderly patients is challenging.

Heterogeneity of age-related physiological changes,(Balducci *et al*, 2000; Balducci & Repetto, 2004; Hurria & Lichtman, 2007; Lichtman, 2004; Merchant & Roy, 2012; Woolthuis et al., 2014) and increased frequency of comorbidities (Salive, 2013; Wedding et al., 2007) suggest that chronological age alone is inadequate to select patients for standard therapy. These factors also affect the ability to maintain chemotherapy intensity and alter life expectancy independent of DLBCL.(Basso et al., 2008; Carson et al., 2015)

No gold-standard definition of frailty exists; but it encapsulates vulnerability to poor recovery after even minor stressor events due to deteriorating physiological systems over a lifetime.(Clegg et al 2013) Frail people are at high risk of adverse events, including falls, disability, institutionalisation and death.(Hubbard & Ng, 2013)

Numerous objective measures of frailty phenotypes have been described, but, in reality, there is a heavy reliance on subjective clinical judgment. The Lymphoma Italian Foundation proposed and prospectively validated an objective a comprehensive geriatric assessment (CGA) in an Italian population age ≥70 years, which was able to identify elderly patients fit enough to benefit from therapies conventionally reserved for younger patients, and could be completed within 15 min (Tucci et al., 2009, 2015). These studies have shown that CGA is superior to clinical judgment in determining which older patients will benefit from curative intent treatment.

We sought to characterize in detail the morbidity associated with rituximab-chemotherapy combinations in a real-world cohort of elderly DLBCL patients, and explore the utility of baseline geriatric assessment (GA) in predicting toxicities and guiding initial dosing strategies.

Methods

Patients aged ≥60 years with newly-diagnosed, biopsy-proven DLBCL between March 2009 and March 2016, who underwent rituximab-based immunochemotherapy were identified from electronic databases at three Australian tertiary institutions. Patients with central nervous system involvement were excluded. Details of baseline demographics, treatment, toxicity and outcomes were collected from institution electronic patient records.

The CGA developed by Tucci et al (2015) was retrospectively applied to categorise patients into fit, unfit and frail groups (Appendix S1) based on age, Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller & Towers, 1991), Activities of Daily Living (ADL; Katz & Akpom, 1976) and Instrumental Activities of Daily Living (IADL; Lawton & Brody, 1969) scores. Briefly, CGA-fit patients were aged <80 years, with no limitations in ADL (score 6/6) and IADL (score 8/8), no severe comorbidities grade 3–4/4 by CIRS-G (excluding haematological comorbidities) and <5 grade 2/4 comorbidities. CGA-unfit patients were aged ≥80 years, with ADL score 5, IADL score 7, no CIRS-G grade 3-4 comorbiditiesand up to 5-8 grade 2 comorbidities. Those not meeting CGA-fit or –unfit criteria were classified CGA-frail. CIRS-G, ADL, IADL and revised International Prognostic Index (R-IPI)(Sehn et al., 2007) were calculated based on data from pre-treatment clinical records. Those with incomplete data for CGA calculation were excluded from the CGA analysis. For CIRS-G, quantifying burden of comorbidities (number 0-14, grade 0-4), a score ≥7 was considered high. ADL (bathing, dressing, feeding, continence, transfer, toileting) and IADL (ability to use telephone, shopping, food preparation, housekeeping, laundry, transportation, handling of finances) scores refer to the number of residual functions in the CGA (lower scores representing increased dependence; Tucci *et al* 2015). Details of death or last follow-up were obtained from clinical records.

Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 were retrospectively applied (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). Dose reduction (DR) was defined as >25% reduction in any part of the standard doses for the baseline planned chemotherapy regimen. Planned baseline chemotherapy regimens included full-dose R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), full-dose R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone; Moccia et al., 2009) or other CHOP-like regimens and standard R-miniCHOP(Peyrade et al., 2011), as it was institutional policy to administer R-miniCHOP for

cycle 1 in all patients aged ≥80 years and patients aged ≥75 years with multiple comorbidities or poor performance status during the study period. Dose delays were defined as delays >5 days due illness or tolerability. Detailed analyses incorporating degree of DR, timing of dose delays, and differences in individual drugs were not performed due to small subgroup sizes limiting meaningful comparison and retrospective procurement of actual drug doses received subject to incomplete documentation. Overall survival (OS) and progression-free survival (PFS) were determined by Kaplan Meier analyses. Response was based on Lugano criteria.(Cheson et al., 2007, 2014) Overall response rate (ORR) included the achievement of either a complete response (CR) or a partial response (PR) at any time. It was not routine practice to perform formal quality of life assessments during the treatment period.

Statistical analyses were performed using IBM Statistics software build 1.0.0.950 (IBM, Armonk, NY, USA). Kendall's tau-c was used to assess associations between CGA groups (fit, unfit, frail) and other variables (Tables I-III). Chi-square analysis or Fisher's exact test was used to compare associations between other categorical variables (Table SI). Logrank test was used to compare survival outcomes between groups. Variables from univariate analyses that had a statistically significant association with survival were included in Cox proportional hazards models for multivariate analyses. Local human research ethics committee approval was obtained at all sites.

Results

Patient characteristics.

Two hundred and five patients were identified (Table I). The median age of this group was 73 years (range 60-97). Fifty (24%) were aged ≥80 years. Baseline CIRS-G was ≥7 in 77/197 (39%) assessable patients and the Eastern Cooperative Oncology Group performance status (ECOG PS) was ≥3 in 13/195 (7%). The CGA (Tucci et al., 2015) classified 57/138 (41%) as fit, 29/138 (21%) as unfit and 52/138 (38%) as frail. We were unable to accurately assign CGA categories to 67/205 (33%) patients due to insufficient information in the medical records. All patients received rituximab-based therapy.

Treatment-related morbidity and survival outcomes.

Clinicians determined that 62% (128/205) patients required admission for Cycle 1 of chemotherapy (medically unsuitable for discharge if diagnosed as inpatient or electively admitted). Seventy-three percent (146/201) of patients experienced grade ≥3 toxicities (Table II); no baseline characteristics predicted for development of grade ≥3 toxicity (Table SI). Eighty-

one percent (163/201) had an admission during treatment, 8% (10/126) required intensive care. Median number of unplanned admissions was 1 (range 0-8) with median duration of hospital stay of 9 days (range 1-83). DR and early cessation of therapy are shown in Figure 1. A prior DR had already occurred in 19/23 (83%) patients who ceased treatment early. Overall, 39/166 (23%) patients had chemotherapy delays. Detailed reasons for DR and delays were not documented. Baseline DR ($p<0.001$ and $p<0.001$), subsequent DR ($p=0.018$ and $p=0.005$) and early cessation of therapy ($p<0.001$ and $p<0.001$) were associated with poorer OS and PFS, respectively.

At a median follow-up duration of 29 months, median OS (56/205 deaths captured) and PFS (69/205 events captured) were not reached, 2-year OS and PFS was 80% and 72% respectively. 3-year OS and PFS was 73% and 65% respectively. ORR was 98% (193/196) and CR rate was 81% (158/196). Fifty-six (56/205, 27%) deaths occurred, 27/56 (48%) due to disease and 12/56 (21%) were treatment-related, with 3 occurring during Cycle 1(1 sepsis, 2 heart failure). The cause of death was unknown in 13 patients.

CGA assessment.

Median ages for CGA-fit, CGA-unfit and CGA-frail patients were 69, 81 and 76 years respectively. Table III displays patient outcomes by CGA groups, including the 2- and 3-year OS and PFS. CGA was associated with baseline DR ($p=0.005$), but not the need for Cycle 1 admission ($p=0.310$), development of grade ≥3 toxicities ($p=0.607$), ≥2 unplanned admissions ($p=0.501$) or subsequent DR ($p=0.139$).. Using Cox regression, after controlling for other parameters, CGA-frail had inferior OS to CGA-fit patients, but there was no significant difference in OS of CGA-unfit and CGA-fit patients (Hazard ratio 1.48, 95% confidence interval 0.56-3.91, $p=0.426$) (Table IV, Figure S1a). Baseline DR and failure to complete planned number of cycles retained prognostic significance for OS following multivariate analysis. Figure S2 shows the inferior OS for patients who had DR at baseline compared to those who did not. After multivariate analysis for PFS, baseline DR and early cessation of therapy retained prognostic significance, but CGA did not (Table IV, Figure S1b).

Discussion

The use of CGA in 138/205 elderly DLBCL patients receiving rituximab-chemotherapy combinations across 3 Australian institutions demonstrates that CGA-fit patients had superior OS compared to CGA-frail patients. CGA had no impact on clinician-determined inpatient administration of Cycle 1 chemotherapy, development of grade ≥3 toxicities, ≥2 unplanned

admissions or subsequent DR; however, CGA score was associated with baseline DR in our cohort. Baseline DR and early cessation of chemotherapy were independently associated with poorer PFS and OS.

Our retrospective CGA assessment highlights the functional heterogeneity within this elderly group (41% CGA-fit, 21% CGA-unfit, 38% CGA-frail). Recent studies have suggested that full dose standard chemotherapy in very elderly DLBCL patients does not improve their survival outcomes.(Carson et al., 2015; Eyre et al., 2016; Juul et al., 2018; Vidal et al., 2018) We suggest that chronological age alone, whilst associated with CGA, did not identify all the CGA-unfit or CGA-frail patients; of those aged 60-79 years in our cohort, 7% and 36% were respectively classified as CGA-unfit or CGA-frail.

Curative chemotherapy can be difficult to deliver in older patients. Our real-world cohort experienced comparable treatment-related mortality (6%) compared to prospective trials,(Habermann et al., 2006; Pfreundschuh et al., 2008) but had higher rates of grade ≥3 infection, hepatotoxicity, nephrotoxicity, anaemia, thrombocytopenia and febrile neutropenia.(Coiffier et al., 2002; Habermann et al., 2006; Merli et al., 2012; Peyrade et al., 2011; Pfreundschuh et al., 2008) This may be because these large trials often excluded patients with inadequate organ function, advanced age (>80 years), poor ECOG PS (3-4), compliance issues and comorbidities, such as viral hepatitis, human immunodeficiency virus infection and recent malignancy. The majority of our cohort also required ≥1 admission, had multiple unplanned admissions or required DR during this outpatient-based therapy, parameters which are poorly described in large clinical trials.

In isolation, common methods of toxicity reporting (such as CTCAE) underestimates morbidity. We found that patients with any IADL impairment were more likely to have multiple admissions (p=0.016), despite not having more frequent grade ≥3 toxicities (Table SI, p=0.564), possibly reflecting poorer tolerance of milder toxicities. For example, anaemia was poorly tolerated, with higher rates of transfusion (78/201, 39%) compared to the rate of grade 3 anaemia (Table II, 27%), also observed in the RICOVER-60 study.(Pfreundschuh et al., 2008) ECOG PS alone incompletely characterised functional deficits; 44/134 (33%) patients with ECOG PS 0-2 had ≥1 IADL loss and 6/155 (4%) had ≥1 ADL loss, supporting the superiority of GA over ECOG PS in characterising function.(Hamaker et al, 2014; Repetto et al., 2002) GA can unmask geriatric issues missed by standard assessment(Hamaker et al., 2014; Horgan et al., 2012) in domains such as ADL, comorbidities, nutrition and mental health, which predict toxicity and mortality in

this population,(Puts et al., 2012) and which need to be addressed early to maximize treatment delivery and minimize treatment-related morbidity.

Performing CGA may guide decisions surrounding dose intensity. Prior data suggest curative-intent treatment may not provide survival benefit over palliative therapy in CGA-unfit or CGA-frail cohorts.(Tucci et al., 2009, 2015) However, 65% of frail patients in our cohort were prescribed R-CHOP, highlighting the inadequacies of clinical assessment alone. Reasons for the lack of benefit were unclear in published CGA-defined series.(Tucci et al., 2009, 2015) However in our cohort, we noted that a substantial proportion of those with severe toxicities (59/100, 59%), unplanned admissions (51/81, 63%), early treatment cessation (17/22, 77%) and treatment-related deaths (8/10, 80%) were CGA-unfit or CGA-frail, although differences between CGA groups and these outcomes were not statistically significant (Table III). Conversely, curative treatment may improve survival in CGA-fit patients.(Tucci et al., 2015) As baseline DR and early therapy cessation were associated with poorer survival outcomes independently of the CGA, it would appear important to optimize delivery of curative chemotherapy particularly for CGA-fit patients (Figure S2) in the absence of contraindications. Improving dose intensity stratification using baseline CGA has potential health economic implications by delivering curative intent treatment only to those who benefit and can tolerate it, reducing admissions and transfusions. Our real-world data can also help patients better understand treatment-related risks and make informed decisions when consenting for therapy.

GA was not routine practice at participating institutions in this study, although multidisciplinary input was recruited according to clinician judgment. Several barriers have potentially led to slow uptake of GA in practice. GA face-to-face consultations take 10-45 min in published reports, hence may be perceived as impractical in resource-poor oncology clinics,(Pfreundschuh, 2010; Puts et al., 2012) Global consensus is lacking on the appropriate patient cohort to assess and tests to utilise. Additionally, GA-related studies lack standardisation,(Puts et al., 2012) and there are insufficient randomised data on optimal methods of interpreting GA results to improve outcomes.(Lin et al, 2017) The only randomised study of GA-adapted treatment suggested that this strategy reduced all-grade toxicity and toxicity-related treatment failures;(Corre et al., 2016) further randomised controlled trials investigating GA-based interventions in oncology patients are now underway.(Mohile et al., 2018) Resource limitations challenge implementation, however engaging patients or carers to self-administer CGA components may overcome this.

There are a number of limitations of this retrospective study. CGA could not be completed in up to a third of patients, reflecting the gaps between current clinical assessments and CGA, leading to potential bias in the analyses. We were not able to prospectively assess the utility of CGA to stratify chemotherapy or to maximise chemotherapy tolerability. It was not possible to capture events that occurred outside our institutions, potentially underestimating toxicity and admission rates. Specific reasons for DR were poorly documented, and subsequent dose escalations were not captured, preventing meaningful analysis of interactions between dosing and other variables. CGA score was associated with baseline DR in our cohort, presumably reflecting clinician assessment of functional status at the time; it is possible that early DR may have masked the impact of CGA on the development of grade ≥3 toxicities or ≥2 unplanned admissions in our analyses. Our cohort also did not take into account elderly patients in whom the decision was made not to initiate treatment.

In conclusion, elderly DLBCL patients receiving combination rituximab-chemotherapy have high rates of grade ≥3 toxicity, high rates of planned and unplanned admissions, and frequent dose reductions. CGA does not appear to predict for increased risk of toxicity in the context of baseline DR. In these older patients, CGA potentially predicts OS and provides additional clinically relevant information beyond current disease-related prognostication (e.g. R-IPI), however prospective studies are needed to confirm if CGA-adapted treatment strategies can minimize morbidity and improve survival outcomes.

Authors Disclosures

Disclaimers:

DMO, MA, GG, ZYN, HH, YSC, BD, ZL, AM: Nothing to disclose. AG: On Roche advisory board for obinutuzumab and subcutaneous rituximab. CYC: Involved in consulting and advisory for Roche, Janssen, Takeda, Merck Sharpe Dohme, Gilead, Bristol Myers Squibb; received research funding from Celgene, Roche, Abbvie; received honoraria (donated to charity) from Roche, Janssen, Takeda, Merck Sharpe Dohme, Gilead, Bristol Myers Squibb; received travel expenses from Roche, Amgen. GC: Receives research funding from Merck Serono, BMS, Hutchison, Pharmacyclics, Novartis, Beigene. EH: Receives research funding from Astra Zeneca, Bristol Myers Squibb, Celgene, Merck KgA, Merck Sharpe Dohme, Gilead, Janssen; on advisory board for Roche, Celgene, Janssen, Merck Sharpe Dohme; receives speaker fees from Takeda, BMS, Janssen; receives travel expenses from Roche, Takeda, Janssen.

Authorship contributions

All authors reviewed and revised the manuscript, and approved of the submitted version. In addition: DMO collected local data, analysed the data and wrote the paper; EH and BD designed the study; MA, GG, ZYN, HH, YSC, ZL and AM collected local data; AG, EH, GC and CC contributed cases.

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Table I. Baseline characteristics, treatment-related parameters and outcomes.

				CGA category				
			All [a]	Fit	Unfit	Frail	Unknown	p-value for interaction
Baseline characteristics	Sex	Female	88	26	16	19	27	NS
		Male	117	31	13	33	40	
	Age, years	60-79	155	57	7	36	55	*<0.001*
		≥80	50	0	22	16	12	
	ECOG PS	0-2	182	56	28	44	54	*0.010*
		≥3	13	1	1	8	3	
	R-IPI	1-2	75	21	20	19	15	NS
		3-5	95	36	9	33	17	
	CIRS-G [b]	<7	120	46	20	18	36	*<0.001*
		≥7	77	11	9	34	23	
	ADL [c]	<6	11	0	1	10	0	*<0.001*
		6	156	57	28	42	29	
	IADL [c]	<8	52	0	13	39	0	*<0.001*
		8	91	57	16	12	6	
Planned regimen	R-CHOP		165	55	16	34	60	*0.055*
	R-miniCHOP		25	0	8	11	6	
	R-CEOP		10	0	3	6	1	
	R-CHEP		2	1	1	0		
	R-CVP		1	0	1	0		
	R-CNOP		1	0	0	1		
	R-PACEBOM		1	1	0	0		
Cycle 1 admission	No		77	11	8	14	44	NS
	Yes		128	46	21	38	23	
Baseline DR	No		143	45	8	29	61	*0.005*
	Yes		59	11	21	23	4	

(a) Includes patients with and without assignable CGA categories. (b) CIRS-G, quantifying burden of comorbidities (number 0-14, grade 0-4), was considered high if ≥7 (c) ADL (bathing, dressing, feeding, continence, transfer, toileting) and IADL (ability to use telephone, shopping, food preparation, housekeeping, laundry, transportation, handling of finances) scores refer to the number of residual functions in the CGA developed by Tucci et al (2015); lower scores representing increased dependence, maximum score 6 and 8 respectively.

ADL: Activities of Daily Living; CGA: comprehensive geriatric assessment; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; DR: dose reduction; ECOG PS: Eastern Cooperative Oncology Group performance status; IADL: Instrumental Activities of Daily Living; NS: Not significant (p≥0.05); R-CEOP: rituximab, cyclophosphamide, etoposide, vincristine, prednisone; R-CHEP: rituximab, cyclophosphamide, doxorubicin, etoposide, prednisone; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CNOP: rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisone; R-CVP: rituximab, cyclophosphamide, vincristine, prednisone; R-IPI: revised International Prognostic Index; R-PACEBOM: rituximab, prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, methotrexate.

Table II. Observed CTCAE Grade ≥3 toxicities.

		CGA category				
	All (%)[(c)]	Fit (%)	Unfit (%)	Frail (%)	Unknown[(d)]	p-value for interaction
Any Grade ≥3 toxicity	146/201 (73)	41/57 (72)	18/29 (62)	41/52 (79)	46/146	NS
Anaemia	55/201 (27)	17/57 (30)	4/29 (14)	14/52 (27)	20/55	NS
Neutropenia	119/201 (59)	33/52 (58)	13/29 (45)	33/52 (64)	40/119	NS
Thrombocytopenia	40/201 (20)	15/57 (26)	1/29 (3)	8/52 (15)	16/40	NS
Febrile neutropenia[(a)]	55/182 (30)	21/57 (37)	5/29 (17)	17/52 (33)	12/55	NS
Raised creatinine	10/200 (5)	1/57 (2)	0/29 (0)	7/52 (14)	2/10	0.022
Raised alanine aminotransferase	16/200 (8)	5/57 (9)	0/29 (0)	4/52 (8)	7/16	NS
Infection	56/199 (28)	17/56 (30)	3/28 (11)	16/52 (31)	20/56	NS
Mucositis	4/201 (2)	2/57 (4)	0/29 (0)	0/52 (0)	2/4	NS
Peripheral neuropathy	5/201 (3)	1/57 (2)	1/29 (3)	2/52 (4)	1/5	NS
Cardiac toxicity	15/198 (8) [(b)]	3/57 (5)	1/29 (3)	4/52 (8)	7/15	NS
Fatigue	14/200 (7)	4/57 (7)	3/29 (10)	4/51 (8)	3/14	NS

(a) Granulocyte colony-stimulating factor was administered in 41%, for primary (27%) or secondary (14%) prophylaxis.
(b) Four died of heart failure or arrhythmia, 3/4 had left ventricular ejection ≤50% pre-treatment (dose-reduced RCHOP 1, R-miniCHOP 2).
(c) Includes patients with and without assignable CGA categories.
(d) Proportion of patients with stated toxicity, that did not have an assignable CGA category.

No patient experienced grade ≥3 nausea or vomiting.

CGA: comprehensive geriatric assessment; CTCAE: Common Terminology Criteria for Adverse Events; NS: Not significant (p≥0.05); R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

Table III. Patient outcomes by CGA categories.

			CGA category				
		All [a]	Fit	Unfit	Frail	Unknown	p-value for interaction
Subsequent DR	No	119	37	16	22	44	0.016
	Yes	82	20	13	30	19	
Early cessation of therapy	No	172	52	22	38	60	NS
	Yes	26	5	5	12	6	
Any grade ≥3 toxicity	No	55	16	11	11	17	NS
	Yes	146	41	18	41	46	
Unplanned admission ≥2	No	98	27	13	17	41	NS
	Yes	107	30	16	35	26	
Overall survival	Median (months)	NR	NR	52	NR		*0.007*
	2-year		90%	71%	56%		
	3-year		82%	60%	53%		
Progression-free survival	Median (months)	NR	NR	53	21		NS
	2-year		79%	64%	65%		
	3-year		66%	58%	46%		
Deaths	Progressive disease	27	6	6	13	2	0.001
	Treatment-related	12	2	3	5	2	
	Unrelated	4	2	1	0	1	

(a) Patients with and without assignable CGA categories included.

CGA: comprehensive geriatric assessment; DR: dose reduction; NR: not reached; NS: Not significant (p≥0.05).

Table IV. Association between baseline variables and OS / PFS.

		Multivariate analysis		
		HR	95% CI	p-value
OS	CGA (reference: fit)			*0.025*
	Unfit vs fit	1.499	0.579-3.881	NS
	Frail vs fit	2.892	1.275-6.559	*0.011*
	Baseline DR	3.387	1.586-7.235	*0.002*
	Subsequent DR	0.671	0.316-1.427	NS
	Early therapy cessation	2.938	1.262-6.838	*0.012*
	Grade ≥3 toxicity	1.754	0.803-3.834	NS
	Cycle 1 admission	1.785	0.723-4.404	NS
PFS	CGA (reference: fit)			NS
	Unfit vs fit	1.197	0.522-2.743	NS
	Frail vs fit	1.913	0.973-3.761	NS
	Baseline DR	2.473	1.297-4.714	*0.006*
	Subsequent DR	0.788	0.406-1.529	NS
	Early therapy cessation	2.304	1.070-4.961	*0.033*
	Grade ≥3 toxicity	2.124	0.990-4.557	NS
	Cycle 1 admission	2.034	0.886-4.668	NS

Log rank was used for univariate analyses. Multivariate analysis utilized the Cox proportional hazards model.

CGA: comprehensive geriatric assessment; CI: confidence interval; DR: dose reduction; HR: hazard ratio; NS: Not significant (p≥0.05); OS: overall survival; PFS: progression-free survival)

Figure legend

Figure 1. Dose modifications including dose reductions and early cessation of therapy (less than planned number of cycles of therapy).

DLBCL: diffuse large b-cell lymphoma; DR: dose reduction.