Impact of relative dose intensity of standard regimens on survival in elderly patients aged 80 years and older with diffuse large B-cell lymphoma

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Supplementary detailed Methods

Study population and clinical information

The inclusion criteria were as follows: newly diagnosed and histologically proven *de novo* DLBCL, aged ≥80 years at the time of diagnosis, and receiving (R-) CHOP or THP-COP (a minimum of one cycle) as the first-line therapy. Exclusion criteria were central nervous system involvement, post-transplant lymphoproliferative disorder, transformed DLBCL, receiving treatment other than CHOP or THP-COP regimens, and receiving radiotherapy after or before chemotherapies. Patients with human immunodeficiency virus infection was also excluded. Baseline demographics including Eastern Cooperative Oncology Group Performance Status (PS), the number of extranodal sites, Ann Arbor stage, elevated lactate dehydrogenase (LDH), serum albumin (Alb),(1) International Prognostic Index (IPI), bulky mass (>7.5 cm), B symptoms, and dementia at diagnosis were collected. Comorbidities and frailties before treatment were assessed by the Charlson Comorbidity Index (CCI) and Geriatric 8 (G8). (2-5) The present investigation was conducted in accordance with the Declaration of Helsinki, and the protocols were approved by the appropriate institutional review boards. Written, informed consent was waived, since this study used retrospective data obtained from hospital records.

Lymphoma classification

Lymphomas were classified using the Revised European American Lymphoma (REAL) classification and the World Health Organization classification. (6)

Treatment regimens

The CHOP regimen consisted of 750 mg/m^2 CPA, 50 mg/m^2 ADR, 1.4 mg/m^2 (maximum 2 mg/body) VCR intravenously on day 1, and 100 mg/body PSL orally or

intravenously on day 1 to 5 every three weeks. The THP-COP regimen was the same as CHOP including the doses, except THP replaced ADR. Dose modification and the timing of the start of subsequent cycles were decided at the physician's discretion. In patients who experienced severe adverse events (AEs) during treatment, each chemotherapeutic drug in the subsequent cycle were reduced and/or the protocol regimen was delayed at the physician's discretion.

Calculation of RDI

DI is an index of a scheduled dose per specific period and calculated using the following formula: planned dose per course (mg/m^2)/planned period per course (weeks). The RDI (%) was calculated by dividing the dose intensity by the respective target dose intensity and multiplying by 100. The average RDI (ARDI) was the average delivered RDI of each chemotherapeutic agent (ADR or THP, CPA, and VCR) of each cycle. A tARDI was the average delivered ARDI of each cycle of the total treatment duration. Six cycles of regimens without any reduction or delay were defined as the maximum value of tARDI 100%. In cases with fewer than six cycles due to progression of disease or death, the number of cycles of regimens actually administered without any reduction or delay were regarded as the maximum value of tARDI 100%. A tARDI <100% indicated that the RDI was less than that aimed for in the protocol.

Outcome measures

The primary outcome was OS. OS was calculated from the date of the diagnosis to the date of death from any cause or the most recent follow-up visit. All patients were divided into two prespecified groups depending on the tARDI, and tARDI of 50% was defined as the cut-off point. (1) The treatment response and toxicities were also evaluated. Complete response (CR),

partial response (PR), stable disease (SD), and progressive disease (PD) were defined according to Cheson's 2007 revised criteria. (7) CR unconfirmed (CRu) was defined according to Cheson's 1999 criteria. (8) Common terminology criteria for adverse events v. 4.0 were used to document treatment related-toxicities. (9) Furthermore, predictors affecting clinician's judgments related to reducing tARDI were also evaluated in a priori analysis.

Statistical analysis

Continuous variables are expressed as median values and range, and differences between groups were assessed using the Mann-Whitney U test. Intergroup differences in categorical variables are expressed as numbers and percentages, and differences between groups were assessed using the chi-squared test or Fisher's exact test. Survival curves for each group by tARDI ≤50% vs >50% were estimated using the Kaplan-Meier method and compared by the log-rank test. Multivariable adjustment was performed for sex, serum Alb, CCI, IPI, G8, and tARDI with a multivariate Cox proportional hazards model for OS. The cut-off score (≤14) of G8 was used in the present investigation. (4, 5) Sensitivity analyses were performed with the substitution of G8. Factors considered to be strongly associated with the prognosis of DLBCL were used. Logistic regression analysis was used to analyze factors that affect severe AEs and reduction of tARDI (≤50%). The presence of a non-linear association between tARDI and all-cause mortality was evaluated using a cox proportional regression model with RCS of 3 and 4 knots. RCS modeling with 3 knots was used because this model showed a better Akaike's information criteria compared with that for restricted 4-knot cubic spline model. The effect of RTX on the relationship between tARDI and OS was assessed by adding an interaction term to the relevant Cox model. A machine learning prediction model, random forest, was also constructed. (10) Random forests yield variable importance measures for the prediction. Variable importance in the random forest model for reduced tARDI (≤50%) was

calculated. Variable importance is a scaled measure having a maximum value of 100. P values were two-sided, and P values < 0.05 were considered significant. For interaction analysis, P value < 0.1 was considered significant. Statistical analyses were performed with R (version 3.4.1, The R Foundation for Statistical Computing, Vienna, Austria) (Team and Computing 2016) or EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan, version 1.37) which is a graphical user interface for R. (11)

Supplementary References

1. 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.

2. Saygin C, Jia X, Hill B, Dean R, et al. Impact of comorbidities on outcomes of elderly patients with diffuse large B-cell lymphoma. Am J Hematol. 2017;92(10):989-996.

3. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383.

4. Kenis C, Decoster L, Van Puyvelde K, et al. Performance of two geriatric screening tools in older patients with cancer. J Clinical Oncol. 2014;32(1):19-26.

5. Sakurai M, Karigane D, Kasahara H, et al. Geriatric screening tools predict survival outcomes in older patients with diffuse large B cell lymphoma. Ann Hematol. 2019;98(3):669-678.

6. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised fourth edition. 2017.

7. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-586.

8. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to

standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999;17(4):1244.

9. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. May 28, 2009 (v4.03: June 14, 2010.). US Department of Health and Human Services., 2010.

10. Wright MN, Ziegler A. ranger: A Fast Implementation of Random Forests for High Dimensional Data in C++ and R. J Stat Softw. 2017;77(1):1-17.

11. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452-458.

Online Supplementary Tables

Online Supplementary Table 1.

Multivariate Cox proportional-hazards analysis of clinical factors significantly associated with overall survival

	Hazard ratio	95% confidence interval	*P* value
Male	1.041	0.589-1.837	0.891
Serum albumin (g/dL)	1.196	0.768-1.862	0.428
CCI score (/point)	1.051	0.878-1.259	0.588
IPI score (/point)	1.973	1.427-2.727	<0.001
tARDI (/10%)	0.889	0.809-0.975	0.013

CCI = Charlson Comorbidity Index. IPI = International Prognostic Index. tARDI = total Average relative dose intensity.

Online Supplementary Table 2.

Multivariate Cox proportional-hazards analysis of clinical factors significantly associated with overall survival

	Hazard ratio	95% confidence interval	*P* value
Male	1.052	0.596-1.856	0.862
Serum albumin (g/dL)	1.193	0.767-1.857	0.433
CCI score (/point)	1.047	0.875-1.254	0.616
Geriatric 8 (≤14)	1.702	0.223-13.020	0.609
IPI score (/point)	1.946	1.404-2.696	<0.001
tARDI (/10%)	0.887	0.809-0.975	0.012

CCI = Charlson Comorbidity Index. IPI = International Prognostic Index. tARDI = total Average relative dose intensity.

Online Supplementary Table 3.

Toxicity

Adverse event (Grade ≥3), n (%)	All patients (N = 127)		tARDI ≤50% (n = 47)		tARDI >50% (n = 80)		*P* value
Hematologic toxicity	100	(78.7)	36	(76.6)	64	(80.0)	0.469
Transfusion (RBCs and/or platelets)	44	(34.6)	18	(38.3)	26	(32.5)	0.561
Febrile neutropenia	58	(45.7)	20	(42.6)	38	(47.5)	0.712
Non-hematological toxicity	52	(40.9)	17	(36.2)	35	(43.8)	0.457
Treatment-related mortality	4	(3.1)	2	(4.2)	2	(2.5)	0.626

RBCs = Red blood cells.

Online Supplementary Table 4.
Logistic regression analysis for non-hematological toxicity and/or febrile neutropenia ≥grade 3 in all patients

	Odds ratio	95% confidence interval	*P* value
(Intercept)	0.051	0.001-1.900	0.107
Male	1.700	0.683-4.210	0.255
Serum albumin (g/dL)	0.957	0.456-2.010	0.907
CCI score (/point)	1.180	0.900-1.540	0.233
IPI score (/pint)	2.190	1.380-3.490	<0.001
tARDI (%)	1.010	0.989-1.020	0.528

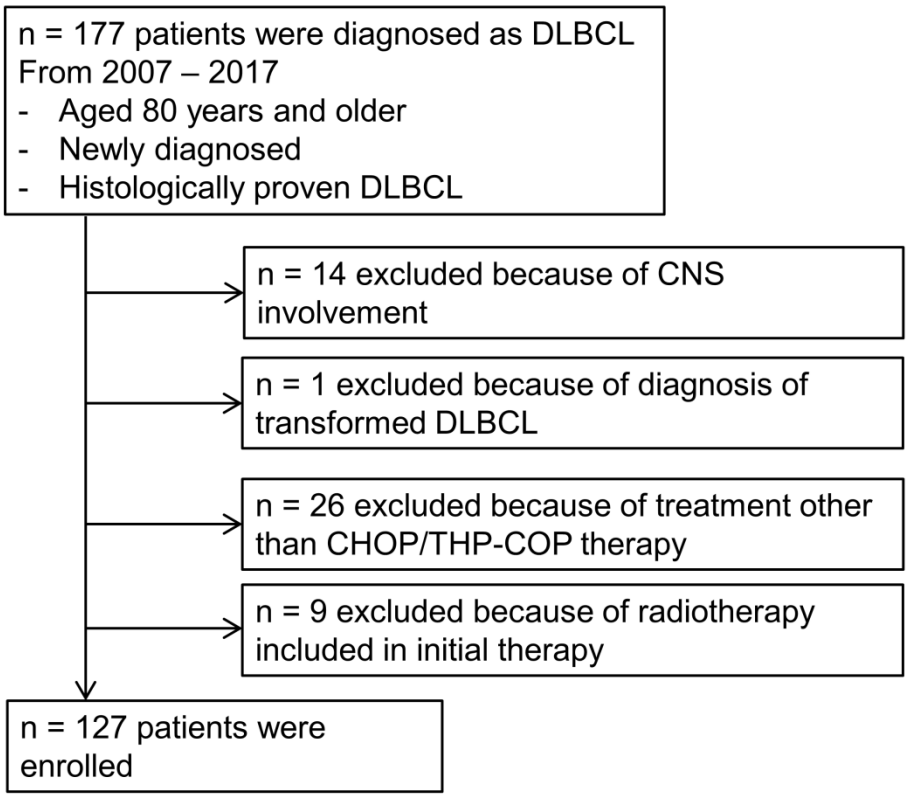
CCI = Charlson Comorbidity Index. IPI = International Prognostic Index. tARDI = total Average relative dose intensity.

Online Supplementary Table 5.

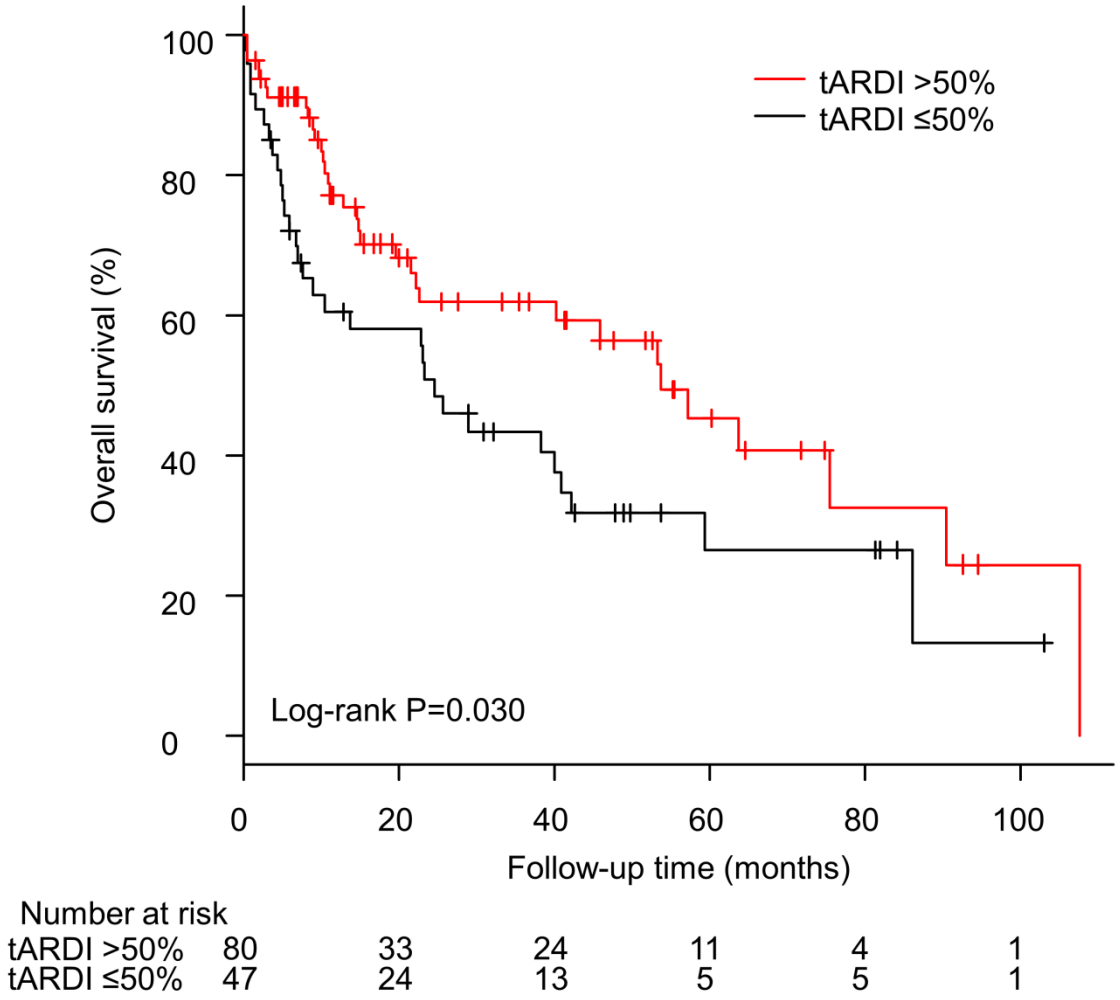
Logistic regression analysis for reduction of tARDI ≤50%

	Odds ratio	95% confidence interval	*P* value
(Intercept)	0.126	0.005-2.980	0.199
Male	1.070	0.472-2.400	0.879
Serum albumin (g/dL)	1.080	0.547-2.140	0.823
CCI score (/point)	1.140	0.908-1.440	0.257
IPI score (/point)	1.230	0.821-1.830	0.317

CCI = Charlson Comorbidity Index. IPI = International Prognostic Index. tARDI = total average relative dose intensity.



Online Supplementary Figure S1. Flow chart of patient selection. CHOP = cyclophosphamide, adriamycin, vincristine, and prednisolone. CNS = central nervous system. DLBCL = diffuse large B-cell lymphoma. THP-COP = cyclophosphamide, tetrahydropyranyl adriamycin, vincristine, and prednisolone.



Online Supplementary Figure S2. Kaplan-Meier plots of overall survival in 127 patients and according to total average relative dose intensity. tARDI = total average relative dose intensity.