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

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

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), and the incidence of DLBCL increases with age.[1] In recent years, world global life expectancy has been increasing impressively and Japan has been challenged with an unprecedented aging society.[2] Consequently, a continuing increase in the incidence of elderly patients with DLBCL is anticipated, and their management is an urgent issue. Although it is widely accepted that maintaining relative dose intensity (RDI) of chemotherapies for DLBCL is crucial for a better prognosis,[3] few studies have focused on the elderly population, despite its importance.[4,5] Two previous phase II study demonstrated the efficacy and safety of approximately 50% of RDI of CHOP (cyclophosphamide [CPA], adriamycin [ADR], vincristine [VCR], and prednisolone [PSL]) with rituximab [RTX),[6,7] but little is known about the efficacy and safety when a higher RDI is provided in this vulnerable population. We report that, even in very elderly patients, there is a considerable number of patients who could achieve a better prognosis owing to maintaining the higher total average RDI (tARDI) of standard regimens, CHOP and THP-COP (CPA, tetrahydropyranyl adriamycin [THP], VCR, and PSL) combined with or without RTX (R-),[8,9] in real-world practice using a Cox hazards model with restricted cubic spline (RCS). The factors affecting the physician's decision to reduce tARDI are age, dementia, elevated lactate dehydrogenase (LDH), the Charlson comorbidity index (CCI), and the international prognostic index (IPI).

To fill the evident gap in the management of very elderly patients in real-world practice, we conducted a retrospective, multicenter investigation at three tertiary institutions in Japan (see the *Online Supplementary Materials and Methods* for details). The impact of the higher tARDI on survival in a pure population of >80 years of age with DLBCL were assessed by the multivariate visual graspable analysis model taking into account the confounding factors. From 2007 to 2017, 177 patients aged ≥80 years at diagnosis were newly diagnosed with DLBCL. A total of 50 patients were excluded due to the exclusion criteria, and the remaining 127 patients were enrolled in the present investigation (*Online Supplementary Figure 1*). The patients' characteristics before the initial treatment are summarized in Table 1. The median ratio of the duration of hospitalization to total treatment duration in the whole study population was 82.9%. Patients in the lower tARDI group had a significant higher ratio of the duration of hospitalization to total treatment duration than in the higher tARDI group (98.7% *vs.* 71.9%, *P*=0.004).

The median follow-up period was 15.4 (range: 0.30-107.6) months, 64 patients (50.4%) died, 38 (29.9%) of whom died of lymphoma, and four (3.1%) of whom died of adverse events (AE). The estimated overall survival (OS) was significantly higher in the tARDI >50% group (*Online Supplementary Figure 2*). The 2-year survival rate was significantly higher in the tARDI >50% group (50.8% *vs.* 61.8%, *P*=0.029). Figure 1 shows the correlation between tARDI and OS. A Cox hazards model with RCS was used, because this non-linear model is more suitable to reflect real-world practice than the linear

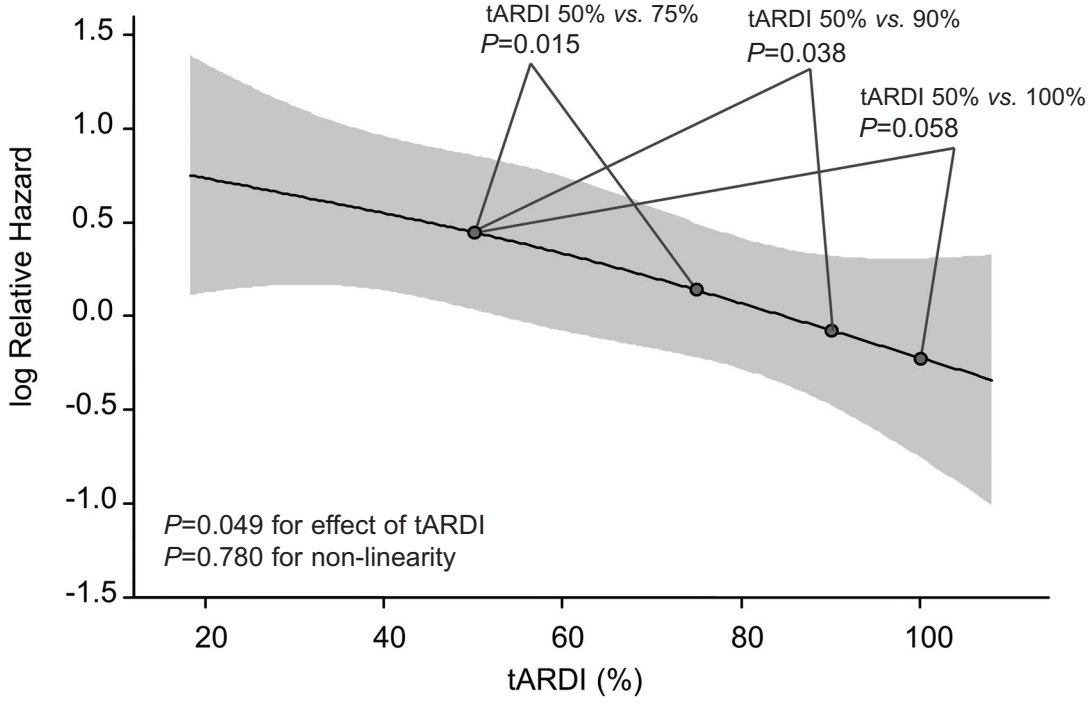

Figure 1. Association between total average relative dose intensity and overall survival in 127 patients by a covariate-adjusted restricted cubic spline hazards model with three knots. The solid line represents the log hazard ratio, and the shaded area is the 95% confidence interval. tARDI: total average relative dose intensity.

Table 1. Patients' characteristics at diagnosis.

	All patients (n=127)		tARDI ≤50% (n=47)		tARDI >50% (n=80)		P	Non-survivor group (n=64)		Survivor group (n=63)		P
Age, year - median (range)	83.7	(80-96)	84.3	(80-96)	83.2	(80-90)	0.008	83.8	(80-96)	83.6	(80-90)	0.127
Male - n (%)	60	(47.2)	25	(53.2)	35	(43.8)	0.359	33	(51.6)	27	(42.9)	0.376
ECOG PS ≥2 - n (%)	60	(47.2)	27	(57.4)	33	(41.2)	0.098	42	(65.6)	18	(28.6)	<0.001
Extranodal sites ≥2 - n (%)	54	(42.5)	24	(51.1)	30	(37.5)	0.143	28	(43.8)	26	(41.3)	0.858
Ann Arbor Stage III/IV - n (%)	100	(78.7)	37	(78.7)	63	(78.8)	0.999	54	(84.4)	46	(73.0)	0.134
Elevated LDH (>ULN) - n (%)	99	(78.0)	34	(72.3)	65	(81.3)	0.272	55	(85.9)	44	(69.8)	0.034
Serum Alb (g/dL) - median (range)	3.1	(1.6-5.1)	3.0	(1.9-4.7)	3.1	(1.6-5.1)	0.739	3.1	(1.6-4.6)	3.1	(1.8-5.1)	0.530
IPI - n (%)												
Low (0, 1)	10	(7.9)	4	(8.4)	6	(7.5)		1	(1.5)	9	(14.3)	
Low intermediate (2)	16	(12.6)	6	(12.8)	10	(12.5)	0.330	7	(10.9)	9	(14.3)	0.018
High intermediate (3)	27	(21.2)	6	(12.8)	21	(26.2)		12	(18.8)	15	(23.8)	
High (4, 5)	74	(58.3)	31	(66.0)	43	(53.8)		44	(68.8)	30	(47.6)	
Bulky mass - n (%)	21	(16.5)	6	(12.8)	15	(18.8)	0.462	13	(20.3)	8	(12.7)	0.341
B symptoms - n (%)	53	(41.7)	17	(36.2)	36	(45.0)	0.357	27	(42.2)	26	(41.3)	0.999
CCI - n (%)												
0	0	(0.0)	0	(0.0)	0	(0.0)		0	(0.0)	0	(0.0)	
1, 2	33	(26.0)	10	(21.3)	23	(28.8)	0.613	12	(18.8)	21	(33.3)	0.131
3, 4	58	(45.7)	22	(46.8)	36	(45.0)		34	(53.1)	24	(38.1)	
≥5	36	(28.3)	15	(31.9)	21	(26.2)		18	(28.1)	18	(28.6)	
Dementia - n (%)	36	(28.3)	19	(40.4)	17	(21.3)	0.026	22	(34.4)	14	(22.2)	0.168
Geriatric 8 - median (range)	9	(2-15)	8	(2-15)	10	(2-15)	0.0682	7.5	(2-15)	10	(3-15)	< 0.001
Without rituximab - n (%)	7	(5.5)	5	(10.6)	2	(2.5)	0.100	7	(10.9)	0	(0.0)	0.013
tARDI -median (range)	58.9	(9.3-134.0)	34.9	(9.6-49.9)	67.5	(50.9-134.0)	<0.001	52.7	(9.6-125.4)	61.4	(19.1-134.0)	0.007
Total RDI of ADR - median (range)	54.8	(3.7-131.0)	31.6	(3.7-51.1)	65.5	(46.3-131.0)	<0.001	50.8	(3.7-115.3)	56.0	(17.3-131.0)	0.012
Total RDI of CPA - median (range)	59.1	(11.4-134.3)	34.0	(11.4-52.2)	67.9	(45.9-134.3)	<0.001	54.2	(5.3-128.9)	61.8	(17.4-134.3)	0.014
Total RDI of VCR - median (range)	59.7	(12.9-136.7)	31.3	(12.9-72.5)	70.3	(33.8-136.7)	<0.001	50.6	(12.9-132.1)	66.1	(13.3-136.7)	0.003
Response, n (%)												
CR / CRu	91	(71.7)	32	(68.0)	59	(73.8)		37	(57.8)	54	(85.7)	
PR	14	(11.0)	4	(8.5)	10	(12.5)		9	(14.0)	5	(7.9)	
SD	3	(2.4)	2	(4.3)	1	(1.2)	0.077	3	(4.7)	0	(0.0)	0.002
PD	13	(10.2)	7	(14.9)	6	(7.5)		12	(18.8)	1	(1.6)	
Not evaluated	6	(4.7)	2	(4.3)	4	(5.0)		3	(4.7)	3	(4.8)	

ADR: adriamycin, Alb: albumin; CCI: Charlson comorbidity index; CPA: cyclophosphamide; CR: complete response; Cru: complete response/ unconfirmed; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LDH: lactate dehydrogenase; PD: progressive disease; PR: partial response; RDI: relative dose intensity; SD: stable disease; tARDI: total average relative dose intensity; ULN: upper limit of normal; VCR: vincristine.

model. A nearly linear association was observed between tARDI and mortality (for non-linearity P=0.780, for effect of tARDI P=0.049). A gradual decrease of risk of mortality as tARDI increased was observed even in the very elderly population. There was no significant interaction between RTX and tARDI for OS (for interaction P=0.143). In the multivariate Cox proportional hazards model for OS, the significant predictors for OS were IPI (hazard ratio [HR] 1.973, 95% confidence interval [CI]: 1.427–2.727, P<0.001]) and tARDI (HR 0.888, 95% CI: 0.809–0.975, P=0.013) (*Online Supplementary Table S1*). The significance of tARDI also persisted in sensitivity analysis (*Online Supplementary Table S2*).

There was no significant difference in severe AE between the two groups according to tARDI (*Online Supplementary Table S3*). Most patients (115 of 127 patients, 90.6%) received primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) including pegfilgrastim, 14 patients (11.0%) received prophylaxis with levofloxacin (LVFX), and 13 patients (10.2%) received prophylaxis with both G-CSF and LVFX. Approximately 20% of the patients (39 of 127) underwent the pre-phase treatment with PSL before conventional-dose chemotherapy. According to a multivariate logistic regression model for grade 3/4 non-hematological toxicity and/or febrile neutropenia, there was no significant association between tARDI and severe AE. The only significant factor associated with severe AE was IPI (odds ratio: 2.19, 95% CI: 1.38–3.49) (*Online Supplementary Table S4*).

To identify the reason for the reduction of tARDI, a multivariate logistic regression model for reduction of tARDI to <50% was performed (*Online Supplementary*

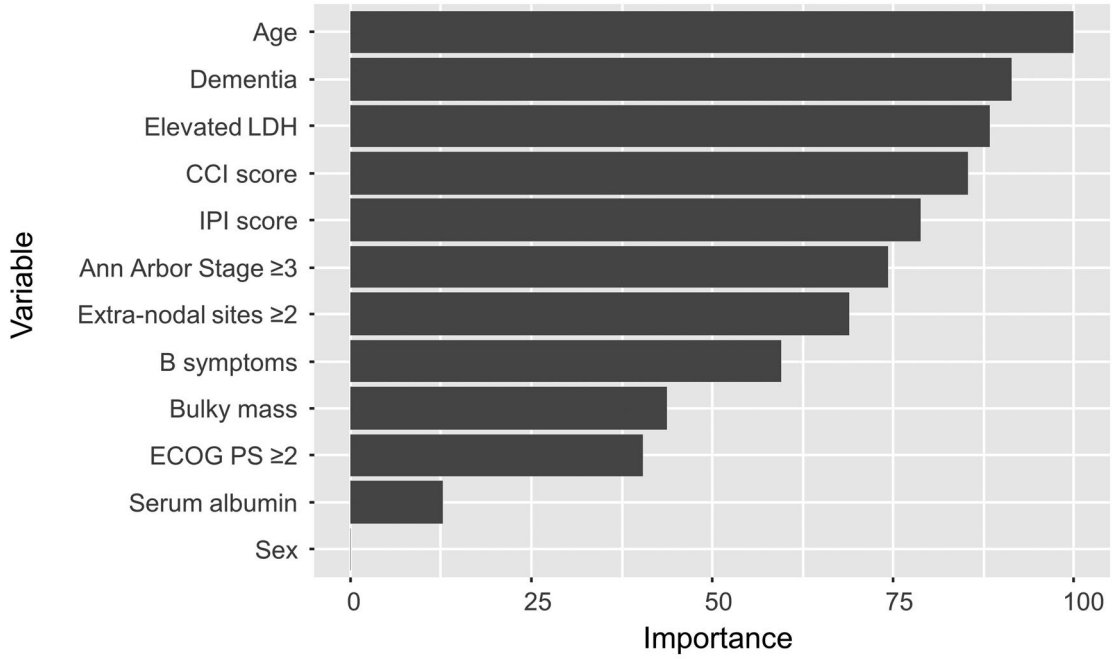

Figure 2. Importance of each predictor for the reduction of the total average relative dose intensity ≤50% in the random forest algorithm. Variable importance is a measure scaled to have a maximum of 100. CCI: Charlson comorbidity index; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LDH: lactate dehydrogenase.

Table S5), but there were no significant predictors, thus a random forest model was created. Figure 2 demonstrates that the variable importance in the random forest model for the reduction of tARDI to <50% were age, dementia, elevated LDH, CCI, and IPI.

The present study demonstrates that providing the higher tARDI of standard regimens can result in better survival even in the elderly population (≥80 years). Of note, at least 80 patients (63%) could safely receive the higher tARDI >50% and achieve a better prognosis. The higher tARDI steadily decreased the mortality risk. The physician's decision to adjust tARDI was affected by age, dementia, elevated LDH, CCI, and IPI.

Two previous phase II trials demonstrated the efficacy and safety of immunochemotherapy with mini-CHOP (approximately 50% RDI) for patients aged >80 years. The 2-year survival in these phase II trials was 59% and 64%, respectively.[6,7] However, the evidence from these trials could not be well generalized to the entire very elderly population because the participants in the clinical trials usually had better conditions, such as a good performance status (PS) <2, than real-world practice. In contrast, half of the participants in our investigation had a PS >2. Despite the frailer population than the previous trials, 2-year OS was 61.8% in the tARDI >50% group. We cannot simply compare the data between a prospective and retrospective study, but this result indicated the efficacy of maintaining higher tARDI was non-inferior to the previous clinical trials. The potential therapeutic advantage of full-dose chemotherapy still remains controversial.[4,5] A Cox hazards model with RCS led to the conclusion that a higher tARDI results in a better OS even in very elderly patients. In our investigation, at least 63% of patients receiving standard regimens could undergo the higher tARDI (>50%). Surprisingly, taking into account the nonlinear representation of RCS, the risk of mortality decreased linearly, was not concave or plateaued, as tARDI increased. In two multivariate Cox proportional hazards models, a remaining independent predictor for OS was tARDI not CCI or the G8 industrialized nation status. This result showed that the impact of tARDI on survival was not simply due to the frailty of the patients.

Indeed, the treatment of very elderly patients can be complicated and result in difficulty maintaining RDI in real-world practice.[4,5,10] In our investigation, considerable number of patients could obtain a better prognosis owing to the maintaining the higher tARDI. This indicates that the physician's judgement when selecting patients fit for the higher tARDI was appropriate. The occurrence of severe AE was not significantly associated with tARDI. A factor affecting the frequency of severe AE was IPI, perhaps because it includes PS, reflecting the frailty. In other words, the frailer patients are the more likely they experience severe AE regardless of tARDI. In the random forest model, age, dementia, CCI, and IPI, which reflect patients' frailty, affected the physician's decision on adjusting tARDI. Physicians are likely to reduce tARDI appropriately depending on their clinical assessment of the risk of severe AE based on the patient's frailty. Treatment-related mortality of the patients aged >80 years through standard regimens for DLBCL was 8%-18%,[4,6] a higher rate than in our investigation (3.1%). This difference can be explained by the fact that nearly all patients were treated as inpatients for a large part of the treatment period and intensive supportive care with prophylaxis with G-CSF including pegfilgrastim and/or LVFX which was supported by the Japanese universal health coverage.[11] Generous support by the Japanese universal health coverage leads to a low socioeconomic inequality in medical care. Most patients who undergo the standard regimens for DLBCL are treated as inpatients at least during the initial cycle for safety sake and commonly elderly Japanese patients are hospitalized. Although some issues such as the medical costs still remain, careful and inten-

sive managements, such as hospitalization, probably enables very elderly patients to receive sufficient RDI. We cannot simply apply the emphasis in our investigation to other countries because Japan is the most advanced "super-aged" society in the world. However, Japan is an epitome of the future of many other developed countries.

In conclusion, maintaining the higher tARDI can achieve a better outcome even in this vulnerable population in real-world practice. Age, dementia, elevated LDH, CCI and IPI affected the physicians' decision-making to reduce tARDI. Surprisingly, at least 63% of patients could safely undergo the higher tARDI >50% and achieve a better prognosis. In the coming global "super-aged" society, a larger cohort is warrant to determine the optimal tARDI and fit-criteria for the higher tARDI.

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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)

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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

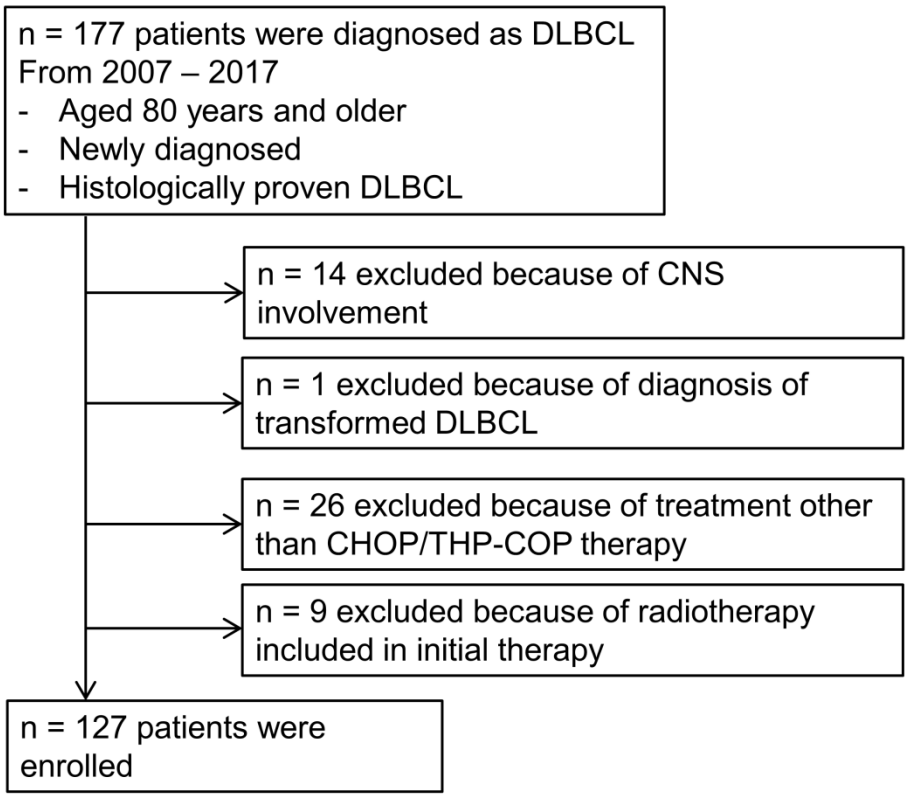
CCI = Charlson Comorbidity Index. IPI = International Prognostic Index. tARDI = total Average relative dose intensity.

Online Supplementary Table 5.

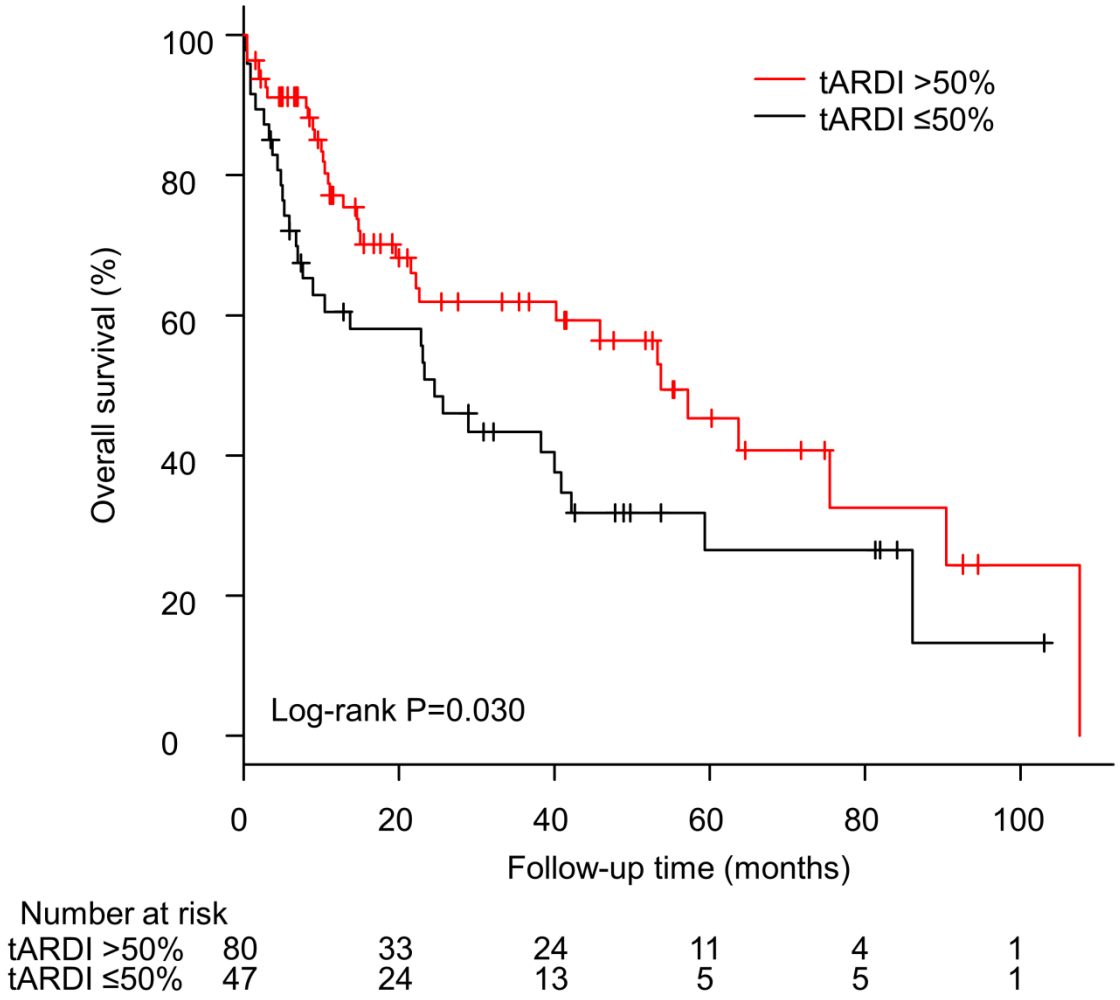
Logistic regression analysis for reduction of tARDI ≤50%

	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.