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Original Article

Extending Treatment Intervals of R-CHOP Therapy Might Be Acceptable for Some Patients with Non-indolent Non-Hodgkin's B-cell Lymphoma

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R-CHOP therapy is generally performed every 3 weeks. We investigated the effects of extending the interval of R-CHOP therapy for >1 week on the prognoses of patients with non-indolent non-Hodgkin's B-cell lymphoma. Among the 338 patients with non-indolent non-Hodgkin's B-cell lymphoma who received initial chemotherapy at our institution, we focused on 178 patients who received R-CHOP therapy and analyzed the outcomes of the patients stratified by the treatment intervals. The estimated 3-year overall survival (OS) for the entire population was 82.1%. Patients treated at intervals of ≥4 weeks were significantly older, and they had significantly longer follow-up periods and lower relative dose intensity. But the estimated 3-year OS was comparable to those treated at <4 weeks (83.3% vs. 80.5% $p=0.947$). In a multivariate analysis, age and the dose of anti-cancer agents had significant impacts on OS, but there was no significant relationship regarding the treatment intervals. Propensity score matching confirmed the same result. R-CHOP therapy every around 4 weeks could achieve relatively good survival in some selected patients with non-indolent non-Hodgkin's B-cell lymphoma.

Key words: R-CHOP therapy, relative dose intensity, non-Hodgkin's lymphoma

R-CHOP therapy, commonly used for aggressive non-Hodgkin's B-cell lymphoma, is generally administered on an outpatient basis at 3-week intervals [1]. Extending the treatment interval could reduce the burden on patients who have difficulty making frequent hospital visits. In contrast to studies focusing on the dosing of agents with R-CHOP therapy, there have been few reports on the treatment intervals so far [2-5]. Therefore, we conducted the present study to retrospectively evaluate the effects of extending the treatment interval of R-CHOP therapy on survival in patients with aggressive non-Hodgkin's B-cell lymphoma.

Patients and Methods

Patients. We reviewed the cases of the 338 patients with non-indolent non-Hodgkin's B-cell lymphoma who underwent initial chemotherapy from March 1, 2005 to March 31, 2020 at the department of hematology in our institution. Of those patients, 178 patients received R-CHOP therapy, which was the most dominant patient population in the cohort. We evaluated the patients' backgrounds, treatment intervals, doses of agents, relative dose intensity (RDI), and prognostic factors including central nervous system (CNS) infiltration or presence of high-risk extranodal lesions. In cases with neither a cerebrospinal fluid examination nor magnetic resonance image examination of the brain, we could not evaluate CNS infiltra-

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tion, and we thus regarded those cases as missing values. The results of the fluorescence *in situ* hybridization (FISH) method were also evaluated in the patients who underwent FISH examinations. The staging and therapeutic response were defined based on the 2014 Lugano classification. In patients who did not undergo a positron emission tomography/computed tomography (PET/CT) examination after their treatment, the therapeutic response was assessed only by CT [6].

We defined a treatment interval as dividing the number of days from the start date of the chemotherapy to 28 days after the last chemotherapy session by the total count of treatments. We defined the start date of the chemotherapy as the start of systemic chemotherapy including cytotoxic anticancer agents or anti-CD20 antibody was administered. The following were not counted in the start date: intrathecal chemotherapy alone for CNS infiltration and a pre-phase administration of steroids to prevent tumor lysis syndrome. The standard dose of R-CHOP therapy consists of 375 mg/m^2 of rituximab for 1 day, 750 mg/m^2 of cyclophosphamide for 1 day, 50 mg/m^2 of doxorubicin for 1 day, 1.4 mg/m^2 of vincristine (up to 2 mg) for 1 day, and 50 mg/m^2 of prednisolone for 5 days, as previously described [1]. The RDI was calculated as previously described [7]. In the present study, we expressed administration ratio of agents (ARA) as the percentage of the actually administered dose per body surface area to the protocol-defined-dose.

We calculated the RDI and ARA as below.

$$\text{RDI} = \frac{\text{Total dose of drug actually administered (mg/m}^2\text{)/actual treatment duration (days)}}{\text{Planned total dose of drug (mg/m}^2\text{)/planned treatment duration (days)}}$$

$$\text{ARA (\%)} = \frac{\text{Total dose of drug actually administered (mg/m}^2\text{)}}{\text{Planned total dose of drug (mg/m}^2\text{)}} \times 100$$

Each patient's body surface area was calculated by the Du Bois formula using the patient's height and weight measured just before the start of each course of chemotherapy [8]. In the calculation of doses of agents and RDI, we did not perform the body surface area correction associated with obesity. This study was approved by the ethical committee of our institution (approval no. 191102).

Statistical analysis. The primary objective of this study was to evaluate the relationship between the treatment intervals of R-CHOP therapy and the patients' overall survival (OS). We also evaluated the relationship between the RDI and ARA of R-CHOP therapy and the patients' OS as secondary objectives. For continuous variables, the normality was tested by the Kolmogorov-Smirnov test. Normally distributed variables are expressed as the mean ± standard deviation and were analyzed by *t*-test. Non-normally distributed variables are expressed as median and range and were analyzed by the Mann-Whitney *U*-test. Discrete variables were analyzed by Fisher's exact test, and the variables that could be converted into binomial variables were subjected to a multivariate analysis by logistic regression analysis. A Kaplan-Meier curve was obtained to represent the survival durations, and a multivariate analysis was performed by Cox proportional hazard regression. A propensity score analysis was used in some analyses with a small case number. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed with EZR ver. 1.53 [9].

Results

In the entire patient population who received R-CHOP therapy, the median age was 67 years, and 53.4% of the patients were male (Table 1). Approximately 80% of the underlying diseases consisted of diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). High-grade B-cell lymphoma (HGBL) and Burkitt lymphoma accounted for only 2.2% in each. Approximately 70% of the cases were at an advanced stage, but groups stratified by the International Prognostic Index (IPI) were relatively distributed in even. 8.4% of the cases had infiltrations of high-risk organs such as testis or kidneys. About 10% of the evaluated cases had MYC gene translocations or MYC protein expression, and 6.1% of the evaluated patients had CNS infiltration. The median treatment interval was 29.08 days, The mean values of ARA and RDI were 90.76%, 0.66 respectively. In addition, 10.1% of the patients received upfront autologous stem cell transplantation (ASCT) following R-CHOP therapy.

The median OS for the entire population was not-reached, and the estimated 3-year OS was 82.1%. The OS was significantly different by IPI stratification. As

Table 1 Patients backgounds

		R-CHOP therapy			
	Group	Overall	≧4week cycle	<4week cycle	*p*-value
		n (%)	n (%)	n (%)	
		178 (100)	114 (64.1)	64 (35.9)	
BL		4 (2.2)	1 (0.9)	3 (4.7)	0.053
DLBCL, NOS		142 (79.8)	98 (86.0)	44 (68.8)	
DLBCL transformed from FL		9 (5.1)	4 (3.5)	5 (7.8)	
DLBCL transformed from LPL		2 (1.1)	1 (0.9)	1 (1.6)	
DLBCL transformed from MALT		2 (1.1)	1 (0.9)	1 (1.6)	
EBV positive DLBCL		5 (2.8)	3 (2.6)	2 (3.1)	
HGBL		4 (2.2)	1 (0.9)	3 (4.7)	
IVL		3 (1.7)	3 (2.6)	0 (0.0)	
PMBCL		4 (2.2)	1 (0.9)	3 (4.7)	
THRBCL		3 (1.7)	1 (0.9)	2 (3.1)	
Sex	Male	95 (53.4)	64 (56.1)	31 (48.4)	0.35
	Female	83 (46.6)	50 (43.9)	33 (51.6)	
Stage (%)	Ⅰ	19 (10.7)	12 (10.5)	7 (10.9)	0.367
	Ⅱ	34 (19.1)	22 (19.3)	12 (18.8)	
	Ⅲ	21 (11.8)	17 (14.9)	4 (6.2)	
	Ⅳ	104 (58.4)	63 (55.3)	41 (64.1)	
IPI	High	47 (26.4)	34 (29.8)	13 (20.3)	0.411
	High-Int	49 (27.5)	32 (28.1)	17 (26.6)	
	Low-Int	45 (25.3)	25 (21.9)	20 (31.2)	
	Low	37 (20.8)	23 (20.2)	14 (21.9)	
involvement of CNS	Yes	3 (6.1)	1 (3.6)	2 (9.5)	0.569
	No	46 (93.9)	27 (96.4)	19 (90.5)	
involvement of testis or breast	Yes	5 (2.8)	3 (2.6)	2 (3.1)	1
	No	173 (97.2)	111 (97.4)	62 (96.9)	
involvement of adrenal or kidney	Yes	10 (5.6)	5 (4.4)	5 (7.8)	0.499
	No	168 (94.4)	109 (95.6)	59 (92.2)	
BCL2 gene translocation	positive	8 (11.8)	1 (3.1)	7 (19.4)	0.058
	negative	60 (88.2)	31 (96.9)	29 (80.6)	
BCL6 gene translocation	positive	16 (25.8)	7 (23.3)	9 (28.1)	0.775
	negative	46 (74.2)	23 (76.7)	23 (71.9)	
MYC gene translocation	positive	12 (26.1)	5 (23.8)	7 (28.0)	1
	negative	34 (73.9)	16 (76.2)	18 (72.0)	
MYC protein overexpression	positive	5 (11.6)	1 (5.3)	4 (16.7)	0.363
	negative	38 (88.4)	18 (94.7)	20 (83.3)	
CD5 protein overexpression	positive	14 (11.9)	10 (13.3)	4 (9.3)	0.571
	negative	104 (88.1)	65 (86.7)	39 (90.7)	
upfront ASCT	Yes	18 (10.1)	10 (8.8)	8 (12.5)	0.446
	No	160 (89.9)	104 (91.2)	56 (87.5)	
Age at diagnosis	year-old	67 [17, 87]	68 [18, 83]	63.50 [17, 87]	0.003
median follow up	days	1,845 [78, 5,219]	2,019 [87, 5,054]	901.50 [78, 5,219]	0.029
treatment intervals	days	29.08 [20.62, 50.50]	30.15 [28.00, 50.50]	27.00 [20.62, 27.88]	<0.001
ARA	%	90.76 [51.99, 107.05]	89.45 [51.99, 102.33]	92.83 [59.81, 107.05]	0.086
RDI		0.66 [0.34, 0.97]	0.63 [0.34, 0.76]	0.74 [0.47, 0.97]	<0.001
WBC	/μL	6,060 [2,270, 21,610]	5,865 [2,270, 21,610]	6,290 [2,350, 13,010]	0.22
Hb	g/dL	12.6 [4.9, 17.5]	12.5 [4.9, 17.5]	12.85 [4.9, 16.7]	0.183
Plt	$\times 10^4/\mu L$	22.55 [4.90, 73.00]	21.05 [4.90, 73.00]	24.20 [5.50, 49.20]	0.015
LDH	U/L	273.5 [24.0, 4,402.0]	271.5 [146.0, 4,402.0]	273.5 [24.0, 4,195.0]	0.807
sIL-2R	U/mL	1,345 [167, 40,000]	1,345 [167, 40,000]	1,260 [229, 27,200]	0.941
β2MG	mg/L	2.5 [1.1, 45.8]	2.45 [1.2, 45.8]	2.5 [1.1, 28.2]	0.86
Alb	g/dL	4.0 [2.2, 5.2]	3.9 [2.2, 5.2]	4.0 [2.7, 5.1]	0.205
Cre	mg/dL	0.72 [0.42, 10.03]	0.72 [0.43, 9.02]	0.70 [0.42, 10.03]	0.625

DA-R-EPOCH, dose-adjusted-R-EPOCH; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MALT, mucosa associated lymphoid tissue; HGBL, High-Grade B cell Lymphoma; IVL, intravascular large B-cell lymphoma; PMBCL, primary mediastinal large-B cell lymphoma; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma; IPI, International Prognostic Index; Int, intermediate; CNS, central nervous system; ASCT, autologous stem cell transplantation; RDI, Relative Dose Intensity; WBC, white blood cells; Hb, hemoglobin; Plt, platelets; LDH, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor; β2MG, beta 2 microglobulin; Alb, albumin; Cre, creatinine.

illustrated in Fig. 1, the estimated 3-year OS for the cases that were High risk, High-Intermediate risk, Low-Intermediate risk, and Low risk by IPI stratification were 63.2% (95% confidence interval [CI]: 45.5-76.5%), 80.7% (95%CI: 66.0-89.5%), 88.4% (95%CI: 74.3-95.0%), and 96.8% (95%CI: 79.2-99.5%), respectively ($p=0.000914$).

To assess the relationship between the treatment intervals of the R-CHOP therapy and the patients' OS, we stratified the patient population into those treated at intervals of ≥4 weeks and those treated at intervals <4 weeks. The patients treated at intervals of ≥4 weeks were significantly older and had longer follow-up periods, lower platelet counts. But there were no significant differences in the other patients' backgrounds, including organ functions that could affect the ARA and RDI.

As expected, the patients treated at intervals of ≥4 weeks had significantly longer treatment intervals and lower RDI values. On the other hand, the stratified analysis by treatment interval showed no significant difference in OS. The estimated 3-year OS was 83.3% (95%CI: 74.8-89.1%) in the patients treated at intervals of ≥4 weeks and 80.5% (95%CI: 67.2-88.8%) in those treated at intervals <4 weeks ($p=0.947$) (Fig. 2A). The results were similar when we stratified the patients into IPI groups ($p=0.586$) (Fig. 2B, C).

In contrast, a stratified analysis by the ARA showed a significant effect on OS. The estimated 3-year OS was 89.3% (95%CI: 82.5-93.5%) in the patients with an ARA ≥80% and 53.1% (95%CI: 34.7-68.5%) in the patients with an ARA <80% ($p=0.00000015$) (Fig. 3A). Similar results were obtained when we stratified the patients into IPI groups ($p=0.0002$) (Fig. 3B, C).

We next analyzed factors that could be prognostic for OS. In the univariate analysis, age, IPI, the ARA, and MYC gene translocation showed significant prognostic effects on OS. But the treatment interval, RDI, expression of MYC protein, and the upfront ASCTs did not have prognostic effects (Table 2). We performed multivariate analysis by the Cox proportional hazard regression using the factors with relatively few missing values in the univariate analysis. In the multivariate analysis, age and the ARA had significant impacts on survival. There was no significant relationship between survival and the treatment intervals (Table 2). The proportional hazard property was maintained ($p=0.76$).

However, there was a possibility of bias by the MYC gene translocation because we could not include the intrinsic prognostic factor in the multivariate analysis due to small case numbers. We thus decided to perform a propensity score analysis.

We first developed a propensity score by using a logistic regression analysis in which we used factors that could affect the treatment intervals: such as age ≥70 years, advanced stage, IPI-High group, an ARA <80%, positive MYC gene translocation, and positive high-risk extranodal lesions including testis or breast. The likelihood ratio test compared with a model that did not include the above-mentioned independent variable showed that the *p*-value was as low as 0.000623 and the area under the receiver operatorating characteristic (ROC) curve was 0.889, showing the usefulness of the model (Fig. 4). In addition, the variance inflation factors were as low as 1.32 at the maximum, indicating low multicollinearity.

We then performed a multivariate analysis by Cox proportional hazard regression together with the treatment intervals and inverse probability of treatment weighting to cope with the decrease in the case number due to matching. Even in this analysis, there was no significant difference in survival with treatment intervals (hazard ratio 0.3643, 95%CI: 0.09612-1.381 $p=0.1375$). The proportional hazard property was maintained in this analysis as well ($p=0.26$).

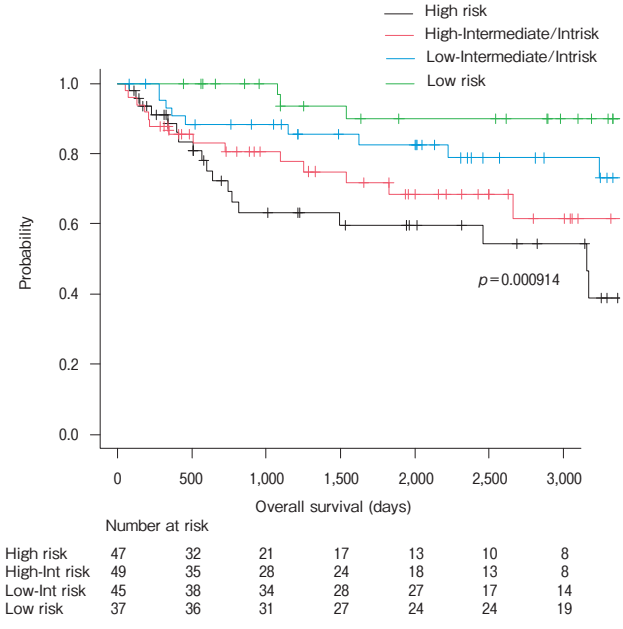

Fig. 1 Overall survival stratified by IPI.

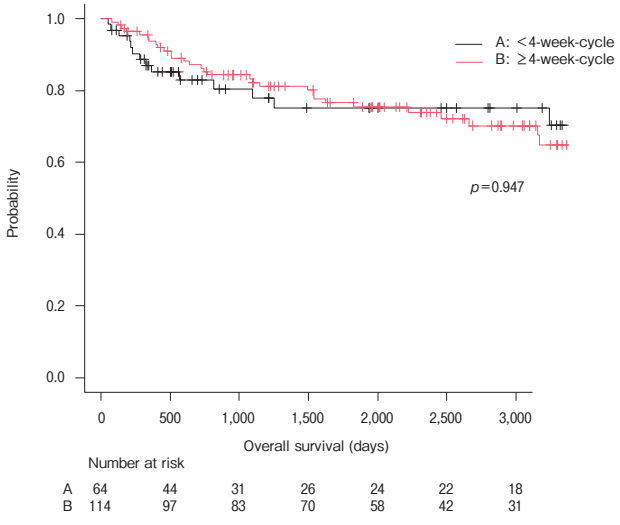

Fig. 2A Overall survival stratified by treatment interval.

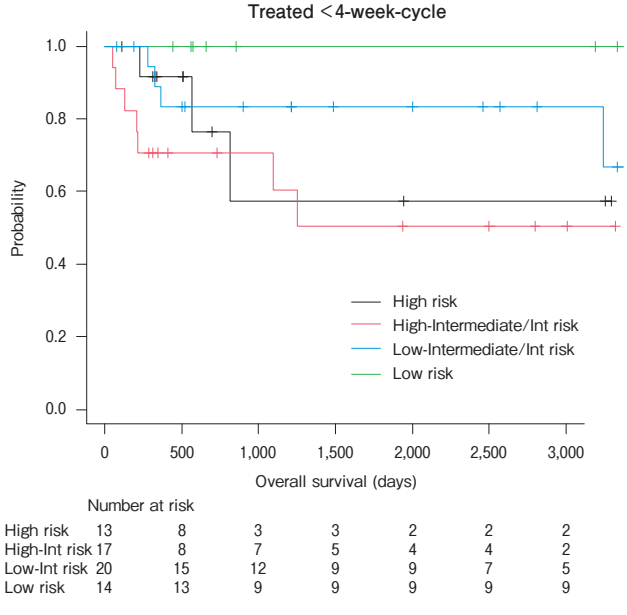

Fig. 2B Overall survival of patients received R-CHOP therapy <4-week-cycle stratified by IPI.

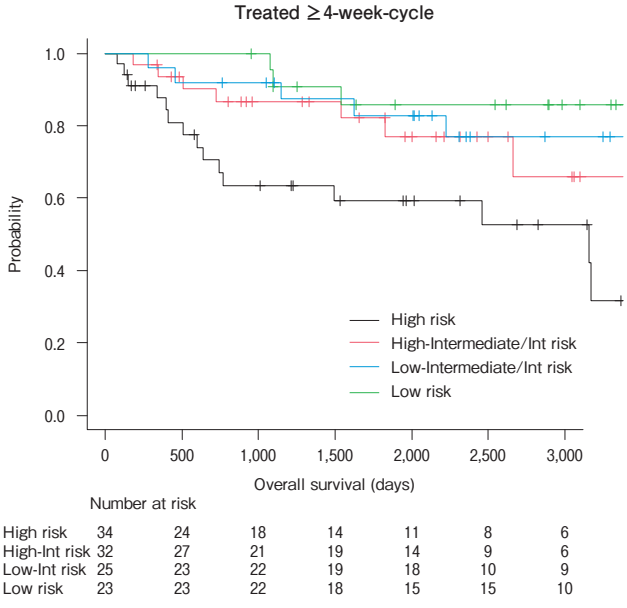

Fig. 2C Overall survival of patients received R-CHOP therapy ≥4-week-cycle stratified by IPI.

Discussion

We obtained relatively good results with R-CHOP therapy performed at intervals of approx. 4 weeks. Interestingly, the stratified analysis by treatment intervals did not show a significant difference in the patients' OS, even though there was a significant difference in the RDI (approx. 10%) between the patients treated at intervals of ≥4 weeks and those treated at intervals of <4 weeks. In earlier studies, even a 10% disparity in the RDI was supposed to make a difference in survival [4,10]. In contrast, the present study's analysis stratified by the ARA showed a significant difference in survival. Therefore, even with the same decrease in the RDI, the effect on the prognosis may differ between a decrease of the ARA and an extension of the treatment interval.

In addition, the underlying disease may affect the relationship between treatment intervals and prognosis. Konishi *et al.* reported no significant correlation between the RDI of R-CHOP therapy and the prognosis of patients with advanced follicular lymphoma [11]. Unlike our result, however, previous studies reported that a lower RDI is associated with worse survival in the treatment of non-indolent non-Hodgkin's B-cell lymphoma [4,5,10,12]. We speculate that the stratification of the underlying disease could have been inadequate in the previous studies, in which indeed they did not mention the use of the FISH method or immunostaining.

DLBCL, accounting for the largest proportion of the underlying disease in our patient cohort, is reported to be heterogeneous in recent studies, and multiple agents are needed in chemotherapy. Ennishi *et al.* reported that the population of DLBCL patients that does not have a genetic profile similar to that of HGBL in a

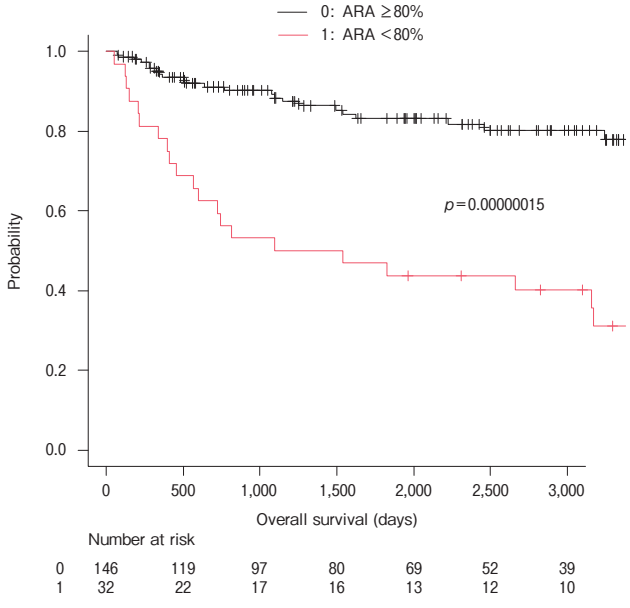

Fig. 3A Overall survival stratified by ARA.

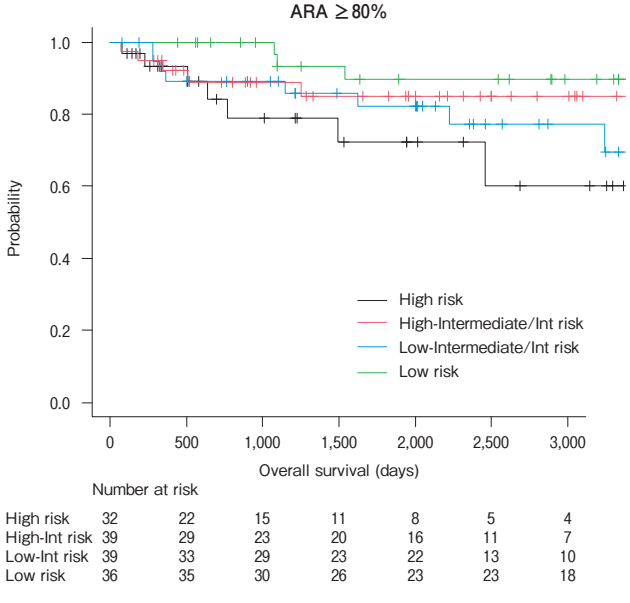

Fig. 3B Overall survival of patients received R-CHOP therapy with ARA ≥80% stratified by IPI.

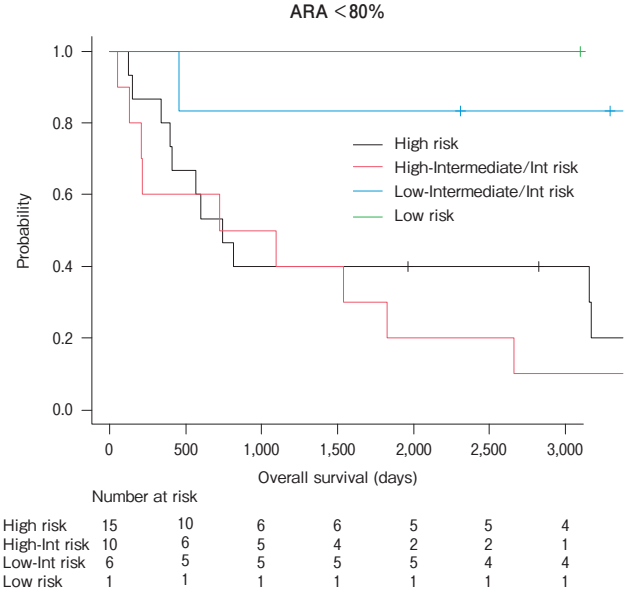

Fig. 3C Overall survival of patients received R-CHOP therapy with ARA <80% stratified by IPI.

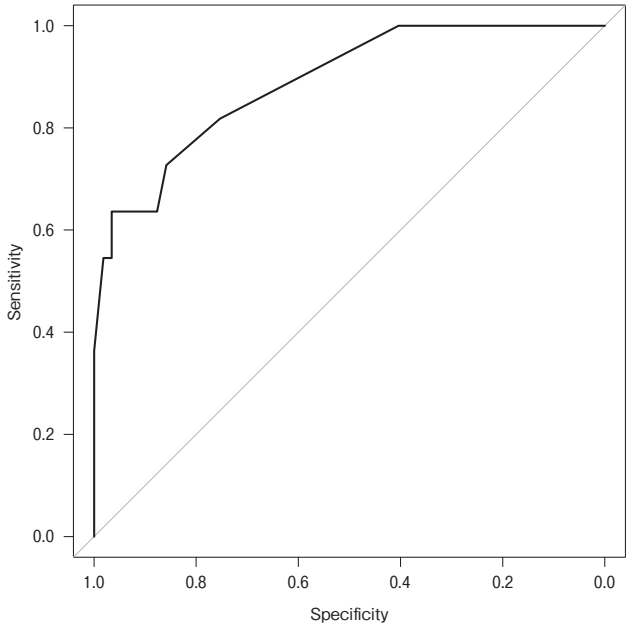

Fig. 4 The receiver operatorating characteristic (ROC) curve.

genome-wide sequence is almost curable with R-CHOP therapy [13]. Unlike the previous studies, our present analyses were able to exclude poor-prognosis populations such as HGBL with the FISH method, which is performable in daily clinical practice, although we could not perform whole-genome sequencing. As a result, we revealed that the effect of the treatment interval on the prognosis was small, and the effect of MYC gene translocation was greater on the prognosis in the univariate analysis.

Taken together, the findings obtained in this study indicate that if the underlying disease is heterogeneous

Table 2 Relationship between clinical factors and overall survival of R-CHOP therapy

	Univariate analysis				Multivariate analysis		
	n	3-year-OS (%)	95%CI	*p*-value	HR	95%CI	*p*-value
IPI: High	47	63.2	45.5–76.5	0.000914			
IPI: High-Int	49	80.7	66.0–89.5		0.8715	0.411–1.848	0.72
IPI: Low-Int	45	88.4	74.3–95.0		0.561	0.198–1.589	0.2765
IPI: Low	37	96.8	79.2–99.5		0.3456	0.06558–1.821	0.2102
with CNS involvement	3	50.0	0.6–91.0	0.911			
without CNS involvement	46	78.7	59.9–89.4				
with adrenal or kidney involvement	10	75.0	29.8–93.4	0.876			
without adrenal or kidney involvement	168	82.5	75.4–87.7				
with testis or breast involvement	5	100.0	NA–NA	0.943			
without testis or breast involvement	173	81.6	74.6–86.9				
MYC translocation positive	8	50.0	15.2–77.5	0.00205			
MYC translocation negative	60	88.7	15.2–77.5				
MYC expression positive	5	53.3	6.8–86.3	0.0819			
MYC expression negative	38	90.9	74.1–97.0				
CD5 expression positive	14	58.0	25.9–80.3	0.13			
CD5 expression negative	104	85.3	76.4–91.0				
dose of agents ≧80%	146	89.3	82.5–93.5	0.00000015			
dose of agents <80%	32	53.1	34.7–68.5		2.23	1.128–4.407	0.02107
RDI of R-CHOP ≧70%	61	85.0	72.1–92.3	0.699			
RDI of R-CHOP <70%	117	80.7	72.0–87.0				
Male	95	80.7	70.8–87.6	0.464			
Female	83	83.9	73.4–90.6				
Stage Ⅰ	19	NA	NA–NA	0.115			
Stage Ⅱ	34	84.1	65.8–93.1				
Stage Ⅲ	21	85.2	60.6–95.0				
Stage Ⅳ	104	77.0	66.8–84.4		1.046	0.6603–1.658	0.8468
with upfront ASCT	18	81.9	53.5–93.8	0.398			
without upfront ASCT	160	82.2	74.9–87.5				
<4week cycle	64	80.5	67.2–88.8	0.947			
≧4week cycle	114	83.3	74.8–89.1		0.5518	0.284–1.072	0.07935
<70 years old	124	91.0	83.9–95.1	0.0000000663			
≧70 years old	54	60.8	45.5–73.1		2.934	1.408–6.115	0.004071

OS, overall survival; CI, Confidence Interval; HR, Hazard Ratio; IPI, International Prognostic Index; Int, intermediate; CNS, central nervous system; RDI, Relative Dose Intensity; ASCT, autologous stem cell transplantation; NA, not applicable.

such as DLBCL, intrinsic prognostic factors like the presence of the MYC gene translocation have a stronger effect on survival than the treatment intervals. Moreover, the appropriate patient selection enabled the selected patients to obtain survival durations comparable to the previously reported 3-week-cycle R-CHOP therapy, even when stratified by IPI [14]. If the panel sequences that are now under development targeting genetic profiles become available in daily settings, we will be able to obtain a superior prognosis stratification than now and low-risk patients with a good prognosis can maintain their quality of life, not only by reducing the number of chemotherapies (which did not exacerbate the prognosis in the FLYER study) but also by reducing the frequent hospital visits with an extension of the treatment intervals [15, 16].

This study has several limitations. First, because it was a retrospective analysis and no specific treatment protocol was defined, we cannot rule out that unknown factors other than those mentioned above may have distorted the results. Second, we could not compare the patients' long-term OS due to shorter follow-up periods in the patients treated at < 4 weeks because most of the cases were concentrated after the approval of pegfilgrastim in Japan in 2014. Third, we could not rule out selection bias, as the FISH method evaluating MYC gene translocation was performed in only about one-third of the patients. Fourth, the results implying the importance of intrinsic prognostic factors are derived from relatively young patient populations and may not apply to older patients whose general condition and comorbidities strongly affect the prognosis [12].

Finally, the histopathology has not been reviewed, and it is possible that the diagnosis of the disease subtype classification could be biased. Verification with a prospective randomized trial is required.

In conclusion, with proper patient selection, R-CHOP therapy every around 4 weeks could achieve relatively good survivals even in patients with non-indolent non-Hodgkin's B-cell lymphoma.

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