Original Article

Treatment Outcomes for Diffuse Large B-Cell Lymphoma in the Rituximab Era: An Evaluation of 193 Patients

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ABSTRACT

Background: Although rituximab, a chimeric anti-CD20 antibody, has been approved as a molecularly targeted drug in Japan, its information is still limited regarding the outcomes of combination chemotherapy including rituximab for treatment of diffuse large B-cell lymphoma (DLBCL).

Methods: Combination chemotherapy including rituximab was administered to 193 of 243 patients who received histopathologic diagnoses of DLBCL at our department from January 2003 through December 2012.

Results: Combination chemotherapy included the R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone; n = 161), R-CHO (rituximab, cyclophosphamide, adriamycin, and vincristine; n = 20), R-HOP (rituximab, adriamycin, vincristine, and prednisolone; n = 1) regimens, and other combination therapy (n = 11). Therapeutic effect was evaluable in all 193 patients. Of the 182 patients treated with R-CHOP, R-CHO, or R-HOP, 140 (76.9%) had a complete response (CR) or unconfirmed CR (CRu), and 5 (2.7%) had a partial response (PR). Four of 11 patients treated with other combination chemotherapy regimens had a CR. Overall, 144 (74.6%) of 193 patients had a CR or CRu, and 5 had a PR; thus, the overall response (OR) rate was 77.2%. The 5-year disease-free survival rates were 72.9% for the 144 patients with CR or CRu, 90.5% for the International Prognostic Index (IPI) low-risk group, 75% in the low-intermediate-risk group, 83.0% in the high-intermediate-risk group, and 68.3% in the high-risk group. There were no significant differences among the 4 IPI groups. The 5-year survival rate was 72.8% overall, 85.2% in the low-risk group, 92.9% in the low-intermediate-risk group, 76.4% in the high-intermediate-risk group, and 49.1% in the high-risk group. The 5-year survival rate in the high-risk group was significantly lower than that in the other groups.

Conclusions: These results show that treatment with combination chemotherapy including rituximab is superior to conventional CHOP or CHOP-like regimens. The validity of IPI, an established prognostic model for DLBCL, appears questionable for regimens with rituximab.

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KEYWORDS: rituximab, diffuse large B-cell lymphoma (DLBCL), R-CHOP, CD20

The CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) regimen was proposed in 1976[1] as a form of combination chemotherapy for aggressive non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBL). The disease-free survival (DFS) rate was later confirmed to be 30% to 40%. In the 1980s, tar-

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geted therapies and more-intensive regimens, the so-called second- and third-generation chemotherapies, were developed to improve upon the CHOP regimen.[2–8] However, no significant differences in treatment outcomes were found in studies comparing the CHOP regimen with these new regimens.[9, 10]

Furthermore, Southwest Oncology Group (SWOG) and Eastern Cooperative Oncology Group (ECOG) conducted large-scale comparative studies of the first-, second-, and third-generation chemotherapies and found no significant differences in rates of complete response (CR), DFS or overall survival (OS), which was confirmed by Fisher et al in 1993.[11] These findings suggest that the practice of administering existing drugs cannot surpass the CHOP regimen and that development of effective new drugs is necessary to improve treatment outcomes.

The molecularly targeted drug rituximab, a chimeric anti-CD20 antibody, was developed by IDEC Pharmaceuticals, Inc. (San Diego, CA, USA) and Genentech inc. (San Francisco, CA, USA) 2 years before the results of the comparative study by Fisher et al.[11] It was approved by the US Food and Drug Administration in November 1997 for clinical use and was expected to improve treatment outcomes for B-cell lymphoma. In Japan, rituximab was approved for the treatment of CD20-positive low-grade or follicular B-cell NHL and mantle-cell lymphoma in March 2001 and for all types of CD20-positive B-cell NHL in September 2003. In this study, we evaluated treatment outcomes for combination chemotherapy including rituximab among patients with DLBCL treated in our department since the approval of rituximab.

Methods

Patients

We analyzed data from 196 patients who were treated with combination chemotherapy including rituximab from among 243 patients in our department who received a histopathologic diagnosis of DLBCL during the period from January 2003 through December 2012. The 47 patients who were not treated with rituximab included 11 who underwent combination chemotherapy before rituximab became available at our hospital, 18 who underwent palliative treatment because of poor general health, 3 with increased hepatitis C virus on a TaqMan® assay, 4 with a positive result for hepatitis B virus (HBV)-deoxyribonucleic acid (DNA) on a TaqMan assay, 5 who died before treatment, 2 with excessive tumor volume, 2 with DLBCL not confirmed to be CD20-positive, 1 who refused treatment, and 1 who was only followed up. Ultimately, 193 patients were evaluable because 3 of the 196 patients developed serious infusion reactions after initial administration of rituximab and were classified as ineligible for treatment with rituximab.

Methods

1. Histopathologic diagnosis

Histopathologic diagnosis was consistent with the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition (2008).

2. Clinical stage

Clinical stage was determined in accordance with the Ann Arbor classification.[12] In addition to clinical stage, the International Prognostic Index (IPI)[13] and revised IPI[14] were also evaluated.

3. Therapy

Combination chemotherapy with rituximab included rituximab + CHOP (R-CHOP; n = 161), R-CHO (rituximab, cyclophosphamide, adriamycin, and vincristine; n = 20), and R-HOP (rituximab, adriamycin, vincristine, and prednisolone; n = 1). Of the 9 patients with a past history of ischemic heart disease or an ejection fraction less than 50%, 5 were treated with R-VP16-COP (rituximab, etoposide, cyclophosphamide, vincristine, and prednisolone), 3 with R-VP16-CO (rituximab, etoposide, cyclophosphamide, and vincristine), and 1 with R-VP16 (rituximab and etoposide). Two patients were enrolled in a collaborative trial with other institutions and were treated with R-THP-COP [rituximab, 4′-O- tetrahydropyranyl adriamycin (therarubicin), cyclophosphamide, vincristine, and prednisolone].

The R-CHOP administration schedule was intravenous infusion of rituximab 375 mg/m^2 on day 1 and the CHOP regimen on day 3 and thereafter. The CHOP regimen included intravenous infusion of cyclophosphamide 750 mg/m^2 and adriamycin 50 mg/m^2 and intravenous injection of vincristine 1.4 mg/m^2 (maximum, 2 mg) on day 1, and oral administration of prednisolone 100 mg/day for 5 days.

4. Assessment of therapeutic effects and evaluation of toxicity

Therapeutic effect was classified as CR, unconfirmed CR (CRu), partial response (PR), stable disease, and progressive disease (PD) in accordance with the International Workshop Criteria.[15] Overall response (OR) was defined as CR + CRu + PR. Interim therapeutic effects were assessed

Table 1 Patient characteristics

Evaluable pts (male/female)	193 pts (108/85)
Median age	68 years (20–91)*
Median follow-up time of surviving pts	38 mos (2–120)*
Clinical stage	[No of pts (%)]
I	30 (15.5)
II	31 (16.1)
III	35 (18.1)
IV	97 (50.3)
B symptom (+)	38 (19.7)
Bulky mass (+)	17 (19.3)
International prognostic index	[No of pts (%)]
Low	48 (24.9)
Low-Intermediate	24 (12.3)
High-Intermediate	62 (32.1)
High	59 (30.1)
Regimen	[No of pts (%)]
R-CHO, R-CHO or R-HOP	182 (94.3)
Others	11 (5.7)
No of courses of R-CHOP, R-CHO or R-HOP	[No of pts (%)]
7 or 8	128 (70.3)
6	25 (13.7)
5 or less	29 (16.0)

*range

pts: patients; mos: months; No: number; R: rituximab; CPM: cyclophosphamid; ADM: adriamycin; VCR: vincristine; PDN: prednisolone; R-CHOP: R, CPM, ADM, VCR, PDN; R-CHO: R, CPM, ADM, VCR; R-HOP: R, ADM, VCR, PDN

after completion of the second or third course. Patients without marked PD continued treatment, and the final assessment was performed after completion of the eighth course or as previously planned. Positron emission tomography (PET) and PET/computed tomography (CT) were performed in 2010 and later, after insurance coverage was approved. Therefore, PET was excluded from the criteria for assessment of effects.

Overall survival (OS) was defined as the period from the beginning of therapy to death, regardless of cause, and DFS was defined as the period from CR attainment to recurrence or death. Toxicity was evaluated in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (2006).

5. Statistical analysis

Survival curves and median survival times were estimated by the Kaplan-Meier method, and differences between groups were evaluated by the log-rank test.

Ethical considerations

This study was reviewed and approved by the institutional ethics committee of Toho University Medical Center, Omori Hospital on May 8, 2014 (Review No. 25-9).

Results

Patient characteristics

The 193 evaluable patients comprised 108 men and 85 women; the median age was 68 years (range, 20–91). The median duration of follow-up among surviving patients was 38 months (range, 2–120). Thirty patients were classified as clinical stage I, 31 as stage II, 35 as stage III, and 97 as stage IV. Among these patients, 38 had B symptoms and 17 had a bulky mass (maximum tumor diameter, ≥10 cm). With regard to the IPI, 48 patients were classified as low-risk, 24 as low-intermediate-risk, 62 as high-intermediate-risk, and 59 as high-risk. Of the 182 patients who received R-CHOP, R-CHO, or R-HOP, 128 received 7

Table 2 Therapeutic effect

	No of pts	CR + CRu	PR	SD or PD	CR + CRu (%)
R-CHOP, R-CHO, R-HOP	182	140	5	37	76.9
R-VP16-COP, R-VP16-CO, R-VP16, R-THP-COP	11	4		7	36.4
Overall	193	144	5	44	74.6

No: number; pts: patients; CR: complete response; CRu: uncomfirmed CR; PR: partial response; SD: stable disease; PD: progressive disease; R: rituximab; CPM: cyclophosphamide; ADM: adriamycin; VCR: vincristine; PDN: prednisolone; ETP: etoposide, R-CHOP: R, CPM, ADM, VCR, PDN; R-CHO: R, CPM, ADM, VCR; R-HOP: R, ADM, VCR, PDN; R-VP-16-COP: R, ETP, CPM, PDN; R-VP16: R, ETP; R-THP-COP: R; THP-ADM, CPM, VCR, PDN

Table 3 5-year disease free survival late

	5-yr DFS (%) (95% CI)
CS (No of pts)	
I (26)	95.5 (71.9–99.4)
II (84)	66.7 (32.4–86.0)
III (28)	95.8 (73.9–99.4)
IV (66)	76.1 (62.0–85.5)
IPI (No of pts)	
L (41)	90.5 (73.3–96.8)
LI (23)	75.0 (45.9–89.9)
HI (51)	80.3 (64.6–92.3)
H (29)	62.5 (44.5–83.6)
Revised IPI	
Best (11)	90.9 (50.8–98.7)
Intermediate (51)	68.1 (49.1–81.3)
Worst (82)	73.9 (59.6–83.8)
Overall (144)	72.9 (71.2–87.2)

yr: year, DFS: disease-free survival, CI: confidence index, CS: clinical stage, No: number, pts: patients, IPI: international prognostic index, L: low, LI: low intermediate, HI: high inter-mediate

or 8 courses, 25 received 6 courses, and 29 received 5 or fewer courses (range, 1–8) (Table 1).

Therapeutic effects

Therapeutic effects were evaluable in all 193 patients, and 140 (76.9%) of the 182 patients who were treated with R-CHOP, R-CHO, or R-HOP had a CR or CRu, and 5 had a PR. The OR rate was 79.6%. Of the 11 patients treated with R-VP16-COP, R-VP16-CO, R-VP16, or R-THP-COP, 4 had a CR or CRu. In total, 144 (74.6%) of 193 patients had a CR or CRu, and 5 had a PR. The OR rate was 77.2% (Table 2).

Disease-free survival

Of the 144 patients with a CR or CRu, 31 relapsed. The 5-year DFS rate was 72.9%, and the DFS curve did not reach the median time (Table 3, Fig. 1). With regard to DFS curves according to clinical stage, the DFS curves for stage I 26, II 24, and III 28 patients did not reach the median time. Median DFS for stage IV 66 patients was 89 months and did not significantly differ among the 4 groups (Fig. 2). The 5-year DFS rate according to IPI was 90.5% in the low-risk group, 75.0% in the low-intermediate-risk group, 83.0% in the high-intermediate-risk group, and 68.5% in the high-risk group. The DFS curves in the low-intermediate- and high-intermediate-risk groups did not reach the median time, and median DFS in the low-intermediate- and high-risk groups was 86 and 99 months, respectively, and did not significantly differ among the 4 groups (Table 3, Fig. 3). The 5-year DFS rate according to the revised IPI was 90.9% in the best group, 68.1% in the intermediate group, and 73.9% in the worst group and did not significantly differ among these 3 groups (Table 3).

All relapses occurred within 5 years (5 in the low-risk group, 8 in the low-intermediate-risk group, 9 in the high-intermediate-risk group, and 9 in the high-risk group). Among the patients with a CR or CRu, 15 died of DLBCL (14 within 5 years) and 7 died of other causes (6 within 5 years) (Table 4).

Overall survival time

The 5-year OS rate was 72.8% overall and 82.3% for patients with a CR or CRu (Table 5). The OS curve for all 193 patients did not reach the median time (Fig. 4). The OS curves for all 193 patients, according to clinical stage, did not reach the median time for stage I, II, and III patients; however, median OS was 92 months for stage IV patients and significantly differed between stage I and IV and III and IV patients ($p = 0.013$ and 0.001, respectively; Fig. 5). The overall 5-year OS rate in relation to IPI was 85.7% in the low-risk group, 93.3% in the low-intermediate-risk group, 77.0% in the high-intermediate-risk group, and 49.1% in the high-risk group (Table 5). The OS curves for

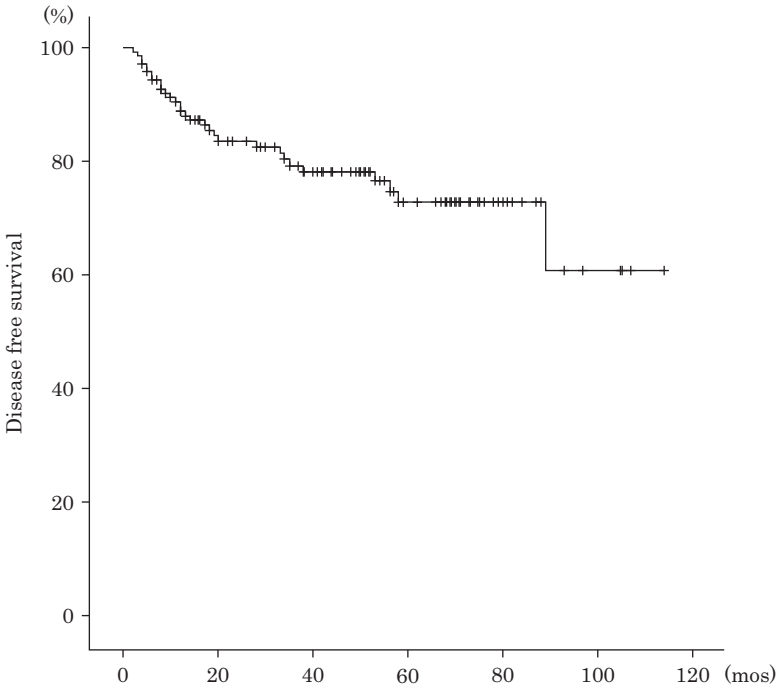

Fig. 1 Disease-free survival (DFS) curve
The 5-year DFS rate for the 144 patients with CR or CRu was 80.6% (95% CI, 71.2% to 87.2%).
CR: complete response, CRu: uncomfirmed CR, CI: confidence index, mos: months

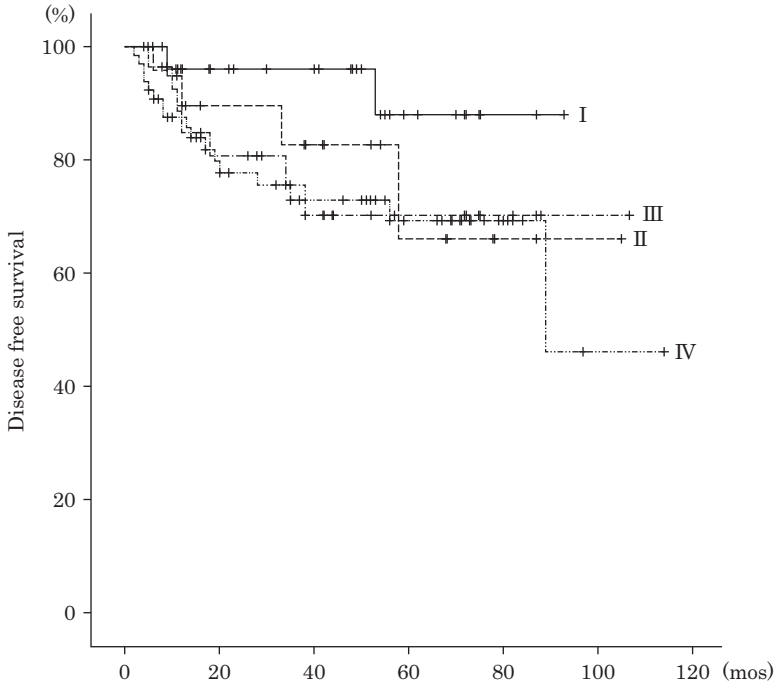

Fig. 2 Disease-free survival curves according to clinical stage (no significant differences among the 4 groups)
mos: months

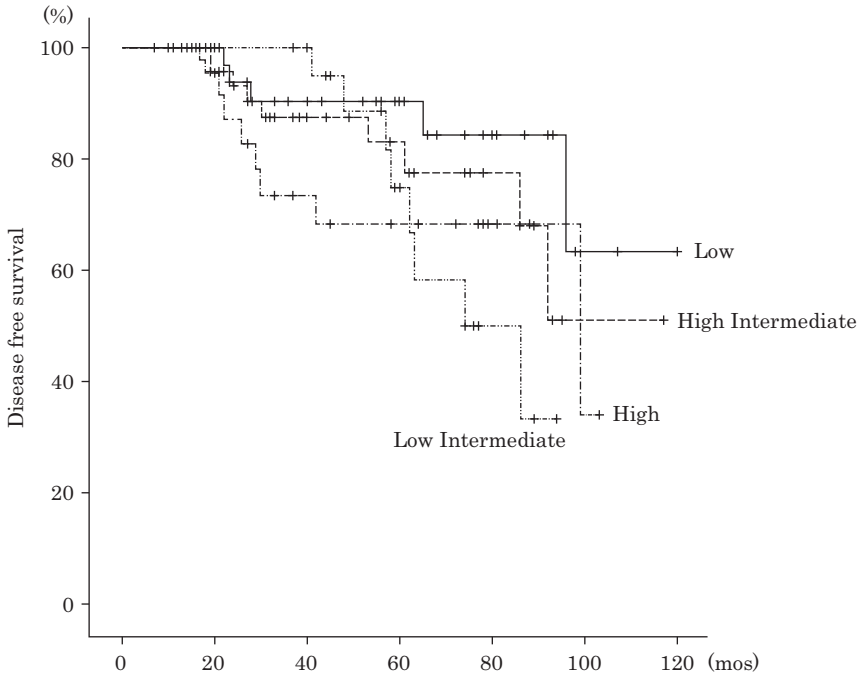

Fig. 3 Disease-free survival curves according to IPI
(no significant differences among the 4 groups)
IPI: international prognostic index, mos: months

Table 4 Events in CR and CRu patients

IPI (No of pts)	Relapse (yrs) (5≦ yrs, 5 yrs<)	Death by DLBCL (yrs) (≦5 yrs, 5 yrs<)	Death by other causes (yrs) (≦5 yrs, 5 yrs<)
L (41)	5 (5, 0)	2 (2, 0)	1 (1, 0)
LI (23)	8 (8, 0)	1 (1, 0)	
HI (51)	9 (9, 0)	6 (5, 1)	2 (2, 0)
H (29)	9 (9, 0)	6 (6, 0)	4 (3, 1)
Overall (144)	31 (31, 0)	15 (14, 1)	7 (6, 1)

CR: complete response, CRu: unconfirmed CR, IPI: international prognostic index, No: number, pts: patients, yrs: years, DLBCL: diffuse large B-cell lymphoma, L: low, LI: low-intermediate, HI: high-intermediate, H: high

the low, low-intermediate-, and high-intermediate-risk groups did not reach the median time, while the median OS time in the high-risk group was 42 months and significantly differed between the high-risk group and the other risk groups ($p<0.001$ for all comparisons; Fig. 6). The overall 5-year OS rate in relation to the revised IPI was 80.0% for the best group, 87.9% for the intermediate group, and 64.3% for the worst group and did not significantly differ among these 3 groups (Table 5).

Toxicity

As described above, 3 of 196 patents developed serious infusion reactions after initial administration of rituximab and discontinued treatment. However, the infusion reactions of the remaining 193 were well controlled, and the second and subsequent courses were administered. Regarding nonhematologic toxicities, hair loss was observed in all patients, grade 1/2 nausea in 49 (25.4%), grade 2/3 peripheral neuropathy in 75 (38.9%), and grade 2/4 constipation in 160 patients (82.9%). Regarding hematologic tox-

icities, grade 1/2 neutropenia was observed in 27 patients (14.0%), grade 3/4 neutropenia in 159 (82.4%), grade 1/2 thrombocytopenia in 74 (38.3%), grade 3 thrombocytopenia in 16 (8.3%), grade 1/2 anemia in 129 (66.8%), and grade 3/4 anemia in 31 (16.1%). Elevated serum aspartate transaminase (AST) and alanine transaminase (ALT) (grades 1 and 2) was observed in 36 (18.7%) and 34 (17.7%) patients, respectively, and grade 3 and 4 elevation was seen in 1 and 2 patients, respectively. Except for the 3 patients with serious infusion reactions, no patients discontinued treatment due to toxicity.

Table 5 5-year overall survival rate

	5-yr OS (%) (95% CI)
CS (No of pts)	
I (30)	88.9 (69.1–96.3)
II (31)	62.1 (31.5–82.2)
III (35)	93.7 (77.0–98.4)
IV (97)	62.9 (51.2–72.6)
IPI (No of pts)	
L (48)	85.7 (68.2–93.9)
LI (24)	93.3 (61.3–99.0)
HI 62)	77.0 (59.9–87.5)
H (59)	49.1 (34.3–62.4)
Revised IPI	
Best (12)	90.0 (47.3–98.5)
Moderate (58)	87.9 (72.6–94.9)
Poorest (123)	64.3 (53.5–73.3)
Overall (193)	72.8 (65.4–79.9)

yr: year, OS: overall survival, CI: confidence index, CS: clinical stage, No: number, pts: patients, IPI: international prognostic index, L: low, LI: low intermediate, HI: high intermediate, H: high

Discussion

CHOP therapy has been the standard therapy for DLBCL. Various other treatments were tried but none surpassed CHOP therapy. New drugs were sought, and rituximab was developed.

Rituximab is a chimeric monoclonal antibody against the CD20 antigen, which is primarily found on the surface of B cells. It is a chimeric monoclonal antibody, including a mouse-derived anti-CD20 antibody in the variable regions of antigen-binding fragment (Fab) and other humanized regions (Fab constant region and crystallizable fragment). Rituximab selectively attacks CD20-positive cells, causing antibody-dependent cytotoxicity, complement injury, and induction of apoptosis.

Because rituximab has a different mechanism of action

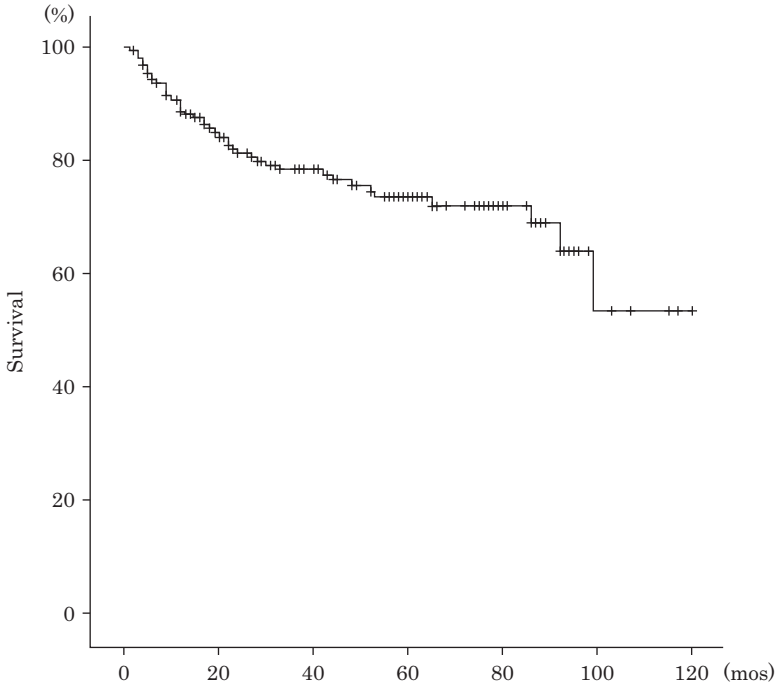

Fig. 4 Overall survival (OS) curve
The overall 5-year OS rate (n = 193) was 73.4% (95% CI, 65.4% to 79.9%).
CI: confidence index, mos: months

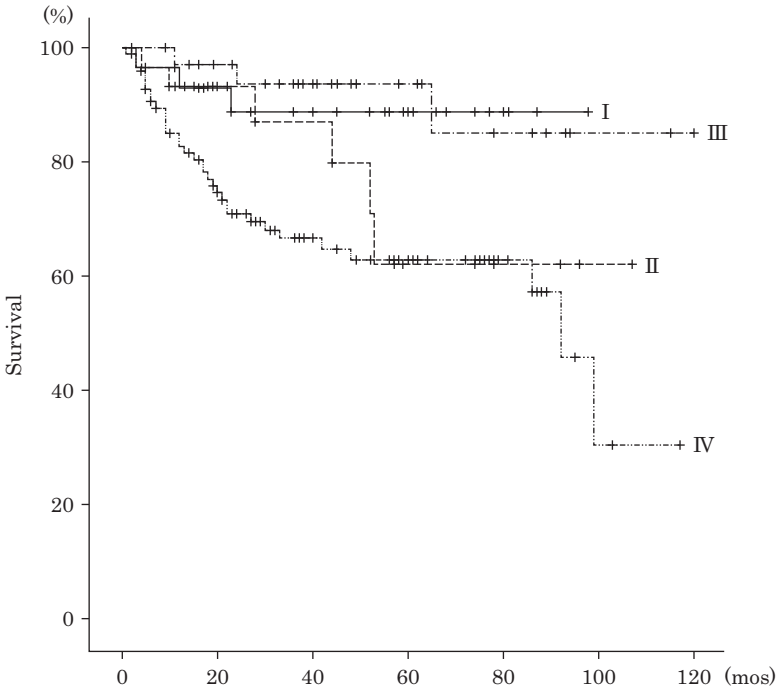

Fig. 5　Overall survival curves according to clinical stage
[There were significant differences between I and IV (p＝0.013) and between III and IV (p＝0.001)]
mos: months

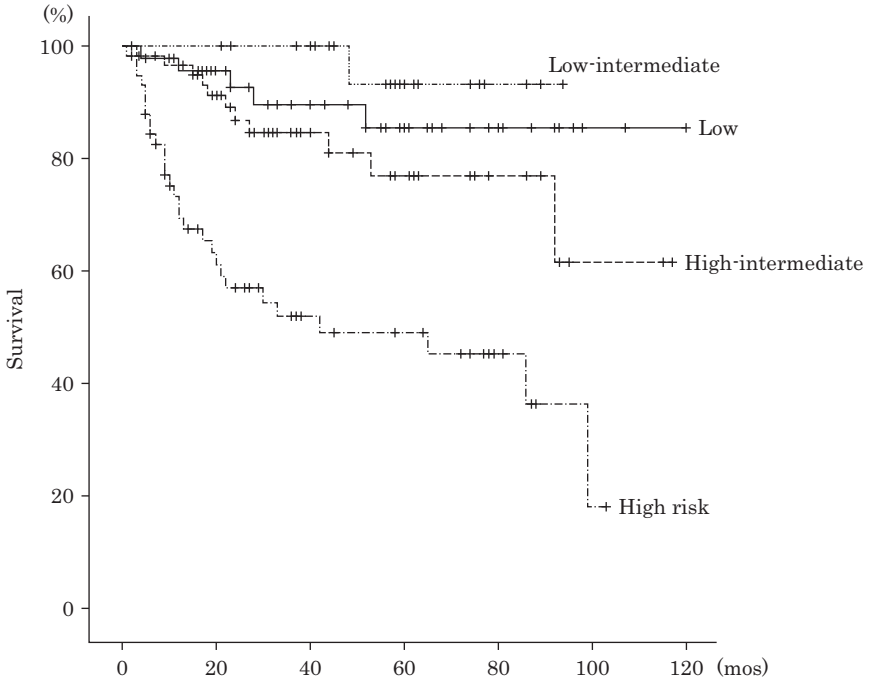

Fig. 6　Overall survival curves according to IPI
(There were significant differences between H and the other groups; p＜0.001 for all comparisons)
IPI: international prognostic index, H: high, mos: months

than those of existing drugs, clinical trials were performed to confirm its role in combination chemotherapy. In a major clinical trial, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) in France compared R-CHOP and CHOP in untreated patients aged 60 to 80 years with clinical stage II-IV DLBCL. The R-CHOP regimen was superior to CHOP in CR rate, 2-year event free survival (EFS) rate, and 2-year OS rate. In a long-term observation, R-CHOP was superior in 10-year OS rate.[16, 17] Furthermore, a retrospective comparative study of patients with DLBCL who received CHOP before administration of rituximab and those who underwent combination chemotherapy with CHOP and rituximab was conducted in British Columbia, Canada. That study found that the 2-year PFS rate improved from 51% to 69% and that the 2-year OS rate improved from 52% to 78%. CHOP with rituximab improved treatment outcomes for DLBCL. Consequently, R-CHOP is now the standard therapy. We started combination chemotherapy including rituximab for patients with DLBCL, when rituximab was approved for treatment of all subtypes of B-cell NHL in 2003.

Regarding treatment outcomes for patients who received a DLBCL diagnosis during 2003–2012, the CR + CRu rate was 74.6%, the 5-year DFS rate was 72.9%, and the 5-year OS rate was 72.8%. This study was not a randomized control trial; therefore, we compared trial outcomes with previous reports. DFS and OS were superior to conventional CHOP or CHOP-like regimens.[1, 9–11]

The prognostic model for DLBCL was developed after analysis of data from 2031 patients with aggressive NHL who underwent combination chemotherapy including adriamycin in the United States, Canada, and Europe in 1993.[13] IPIs comprise 5 clinical factors: age 61 years or older, clinical stage III/IV, ≥2 extranodal lesions, performance status ≥2, and serum lactate dehydrogenase above the normal range. An IPI of 0–1 is classified as low risk, 2 as low-intermediate risk, 3 as high-intermediate risk, and 4–5 as high risk.

IPIs are the standard for prognostic scoring. In this study, we evaluated treatment outcomes and found no significant difference in 5-year DFS among the 4 groups. In our series, 5-year OS was lower in the high-risk group than in the other groups, but there was no significant difference among the other 3 groups. These results suggest that conventional IPIs have questionable validity for comparing outcomes and therapeutic planning, because of improvement in treatment results in the rituximab era. Analysis of outcomes for 365 patients with DLBCL who were treated with R-CHOP in British Columbia revealed that the 4-year PFS and OS rate were 86% and 82%, respectively, in the low-risk group, 80% and 81% in the low-intermediate-risk group, 57% and 49% in the high-intermediate-risk group, and 51% and 59% in the high-risk group. These results indicate that the conventional IPI distinguishes only 2 groups rather than the 4 groups originally described. Consequently, patients with no IPI factors had the best outcomes (4-year PFS and OS rate: 85% and 94%), patients with 1 or 2 factors had intermediate outcomes (80% and 79%), and patients with 3–5 factors had the worst outcomes (53% and 55%).[14] Although we also analyzed treatment outcomes for our subjects according to the revised British Columbia IPI, the 5-year DFS and OS rates were 90% and 90% in the best group, 87.9% and 87.9% in the intermediate group, and 77.3% and 71.9% in the worst group. There were no significant differences among the 3 groups. In the British Columbia study, aggressive lymphoma was targeted, and diseases other than DLBCL were included. Accordingly, the results of our study targeting only DLBCL suggest that DLBCL should be investigated separately from aggressive lymphoma with respect to the outcome-prediction model. Our results revealed no significant differences in scores using IPI or revised IPI. In our study of 245 DLBCL cases, 193 patients (78.8%) received R-CHOP therapy. The IPI and revised IPI appear not to be useful for evaluation of limited R-CHOP therapy.

Our results indicate that introduction of rituximab has markedly improved clinical outcomes of DLBCL. Thus, reassessment of prognostic stratification is required.

Conflicts of interest (COI): The authors have no conflict of interest to disclose.

References

1) Mckelvey EM, Gottlieb JA, Wilson HE, Haut A, Talley RW, Stephens R, et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer. 1976; 38: 1484-93.
2) Fisher RI, DeVita VT Jr, Hubbard SM, Longo DL, Wesley R, Chabner BA, et al. Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. Ann Intern Med. 1983; 98: 304-9.
3) Laurence J, Coleman M, Allen SL, Silver RT, Pasmantier M. Combination chemotherapy of advanced diffuse histiocytic lymphoma with the six-drug COP-BLAM regimen. Ann Intern Med. 1982; 97: 190-5.
4) Skarin AT, Canellos GP, Rosenthal DS, Case DC Jr, MacIntyre JM, Pinkus GS, et al. Improved prognosis of diffuse histiocytic

and undifferentiated lymphoma by use of high dose methotrexate alternating with standard agents (M-BACOD). J Clin Oncol. 1983; 1: 91-8.
5) Dana BW, Dahlberg S, Miller TP, Hartsock RJ, Balcerzak S, Coltman CA, et al. m-BACOD treatment for intermediate- and high-grade malignant lymphomas: a Southwest Oncology Group phase II trial. J Clin Oncol. 1990; 8: 1155-2.
6) Longo DL, DeVita VT Jr, Duffey PL, Wesley MN, Ihde DC, Hubbard SM, et al. Superiority of ProMACE-CytaBOM over ProMACE-MOPP in the treatment of advanced diffuse aggressive lymphoma: results of a prospective randomized trial. J Clin Oncol. 1991; 9: 25-38.
7) Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann Intern Med. 1985; 102: 596-602.
8) Boyd DB, Coleman M, Papish SW, Topilow A, Kopel SK, Bernhardt B, et al. COPBLAM III: infusional combination chemotherapy for diffuse large B-cell lymphoma. J Clin Oncol. 1988; 6: 425-33.
9) Gordon LI, Harrington D, Anderson J, Colgan J, Glick J, Neiman R, et al. Comparizon of second-generation combination chemotherapy regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. N Engl J Med. 1992; 327: 1342-9.
10) Cooper IA, Wolf MM, Robertson TI, Fox RM, Matthews JP, Stone JM, et al. Randomized comparison of MACOP-B with CHOP in patients with intermediate-grade non-Hodgkin's lymphoma. J Clin Oncol. 1994; 12: 769-78.
11) Fisher RI, Gynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med. 1993; 328: 1002-6.
12) Carbone PP, Kaplan H, Musshoff K, Smithers DW, Tubiana M, et al. Report of committee on Hodgkin's disease staging classification. Cancer Res. 1971; 31: 1860-1.
13) Shipp MA, Harrington DP, Anderson JR, Armitage JO, Bonadonna G, Brittinger G; The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993; 329: 987-94.
14) Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol. 2005; 23: 5027-33.
15) Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25: 579-86.
16) Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Femé C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005; 23: 4117-26.
17) Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006; 24: 3121-7.