Randomized phase II study of concurrent and sequential rituximab and CHOP chemotherapy in untreated indolent B-cell lymphoma

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CHOP combined with rituximab (R-CHOP) is regarded as one of the most effective treatments for indolent B-cell non-Hodgkin lymphoma (B-NHL), however, its optimal combination schedule remains unknown. We performed a randomized phase II study to explore a more promising schedule in untreated, advanced indolent B-NHL. Patients were randomized to receive either six courses of CHOP concurrently with rituximab (Arm C), or six courses of CHOP followed by six courses of weekly rituximab (Arm S). A total of 69 patients received the concurrent (*n* = 34) or sequential (*n* = 35) regimen. Overall response rate (ORR) in Arm C was 94% (95% confidence interval [CI], 79 to 99), including a 66% complete response (CR) compared with 97% (95% CI, 85–100), including a 68% CR in Arm S. Patients in Arm C experienced more grade 4 neutropenia (85% *versus* 70%) and experienced more grade 3 or greater non-hematological toxicities (21% *versus* 12%). Both arms were tolerated well. With a median follow-up of 28.2 months, the median progression-free survival (PFS) time was 34.2 months in Arm C, and was not reached in Arm S. R-CHOP is highly effective in untreated indolent B-NHL, either concurrent or in a sequential combination. Both combination schedules deserve further investigation. (*Cancer Sci* 2006; 97: 305–312)

Indolent non-Hodgkin lymphomas (NHLs), in which the representative type of lymphoma is follicular lymphoma (FL), are characterized by an advanced stage at presentation, lack of symptoms associated with the disease, and indolent behavior in terms of the time to symptomatic disease progression.[1,2] Although many chemotherapeutic agents and combination therapies are used in the treatment of patients with FL, a large majority of these patients remain incurable.[3–5] Thus, more effective strategies are needed to overcome the current therapeutic limitations. Rituximab is a chimeric monoclonal anti-CD20 antibody that can deplete malignant B cells through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC),[6] and apoptotic mechanisms.[7] It has also been shown to sensitize lymphoma cell lines resistant to cytotoxic drugs.[8] In recent years, it was demonstrated that rituximab is an active agent against indolent B-NHL and has become a standard component of first-line therapy, either as a single agent or in combination with chemotherapy.[9–18] Recently, the addition of rituximab to the cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) regimen or cyclophosphamide, vincristine and prednisolone (CVP) regimen was demonstrated to improve the clinical outcome in patients with previously untreated advanced FL, without increased toxicity. Czuczman *et al*. conducted the first phase II study on the combination of rituximab with CHOP in mostly untreated patients with low-grade B-NHL or FL.[14] They treated the patients with six cycles of standard CHOP given at 3-week intervals along with rituximab administered twice before, during and after the six cycles of CHOP therapy. All treated patients ($n = 38$) responded with a complete response (CR) rate of 87%, and the median time to progression (TTP) was 82.3 months.[15] Marcus *et al*. reported significant superiority of CVP plus rituximab (R-CVP) over CVP for previously untreated patients with advanced FL in a randomized phase III study.[18] From the viewpoint of the possible synergistic effect between rituximab and chemotherapeutic drugs, it seems to be reasonable that rituximab be delivered in combination with chemotherapeutic drugs concurrently. Whereas, from the viewpoint of enhancing the ADCC effect, which is one of the putative antitumor mechanisms of rituximab, it seems reasonable that rituximab be administered in situations in which effector cells such as macrophages, natural killer cells and neutrophils are intact, in other words, there are no cytotoxic or immunosuppressive effects of chemotherapeutic drugs. Thus, to maximize the

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possible ADCC effect, it might be preferable that rituximab be delivered to patients after recovery from the toxic or immunosuppressive effect of chemotherapy. However, the optimal schedule for the combined use of rituximab and chemotherapy remains unclear. To explore a more promising regimen of rituximab combined with CHOP therapy for the treatment of indolent B-cell NHL, we conducted a randomized phase II trial.

Materials and Methods

Patients

Between July 1999 and July 2000, 69 patients with newly diagnosed indolent B-cell NHLs were enrolled. Eligibility criteria included: aged between 20 and 70 years; a histopathological diagnosis of indolent B-NHL according to the Revised European-American Lymphoma (REAL) classification[19] (including small lymphocytic lymphoma, lymphoplasmacytic lymphoma, FL or marginal zone B-cell lymphoma); no previous treatment; stages III or IV disease according to the Ann Arbor staging system;[20] CD20 positive lymphomas confirmed by immunohistochemistry or flow cytometry; an Eastern Cooperative Oncology Group (ECOG)[21] performance status (PS) of 0, 1 or 2; negative for the hepatitis B virus surface antigen, hepatitis C virus antibody or human immunodeficiency virus antibody; having no other malignancies and normal renal, pulmonary and hepatic function. Approval was obtained from the local institutional review boards of all participating institutions. Informed consent was obtained from all patients before enrollment in accordance with the Declaration of Helsinki.

Study design

This randomized phase II study was designed as a two arm parallel phase II study. The expected overall response rate (ORR) (P1) for either arm was set at 95% based on the phase II study by Czuczman *et al*. where CHOP was combined with rituximab,[14] while the threshold response rate (P0) was set at 75%, based on previous reports on CVP or COP, CHOP or CHOP-like studies.[22] The number of patients required for this study was 27 per arm, calculated in accordance with Fleming's two-stage testing procedure,[23] at $\alpha = 0.05$ (two-side) and $1-\beta = 0.8$. Assuming that up to 20% of patients might be ineligible due to inaccurate histopathological diagnosis at participating institutions, we planned to enroll at least 34 patients per arm. From the viewpoint of selection design by Simon *et al*.,[24] the selection of one arm showing a 15% higher percentage CR at 90% probability would be possible with this number of patients, if the percentage CR of both arms would achieve at least 65%.

Treatment schedule

Patients fulfilling the inclusion criteria were randomly assigned to either the concurrent arm (Arm C) or sequential arm (Arm S) at the independent randomization center, thereby minimizing the bias between the arms regarding PS, clinical stage and institution. All patients were treated with six courses of standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, i.v., day 1; doxorubicin 50 mg/m^2 i.v., day 1; vincristine 1.4 mg/m^2 [capped at 2 mg] i.v., day 1; and prednisolone 100 mg, p.o., days 1–5) every 3 weeks. In addition, patients allocated to Arm C received rituximab (375 mg/m^2 i.v.) 2 days prior to each CHOP cycle, whereas patients allocated to Arm S received rituximab (375 mg/m^2, weekly six times, i.v.) 4 weeks after completion of the sixth cycle of CHOP. Rituximab was given intravenously based on the preceding phase I study in Japan.[25]

Patient evaluation, end-points and response criteria

Patients were observed until the progression of lymphomas or death. Tumor restaging was performed at approximately 3-monthly intervals for the first 12 months and every 4 to 6 months thereafter.

The primary end-point of this study was an ORR in all eligible patients, that is, the percentage of patients achieving a CR, CRu, or partial response (PR), evaluated according to the International Workshop Response Criteria for NHL.[26] CR required the disappearance of all detectable clinical and radiographic evidence of disease, disappearance of disease-related symptoms, and normalization of biochemical abnormalities. Adenopathy on computed tomography (CT) scans must have regressed to normal size (1.5 cm or less in the greatest transverse diameter). CRu was defined as complete disappearance of all detectable clinical and radiographic abnormalities of the disease, with the exception of the presence of a residual adenopathy larger than 1.5 cm, as long as the sum of products of the greatest diameters (SPDs) of the adenopathy had decreased by more than 75%. Residual bone marrow abnormalities, that included increased number or size of lymphoid aggregates without definite cytological evidence of persistent lymphoma, could also be present in patients in the CRu response category. PR was defined as a greater than 50% decrease in the SPDs of the largest dominant nodes or nodal masses. Stable disease patients were defined as having any response that was less than a PR or an increase in the SPDs by less than 25%, with no new lesions appearing. Progressive disease was defined by an increase of more than 25% in the size of the SPDs of the measured lesions, or the appearance of new lesions. All cases were centrally reviewed radiographically using CT films.

Secondary end-points were percentage CR, including percentage CRu and a progression-free survival (PFS) for all eligible patients, as an interval from the day of enrollment to the first day when tumor progression or death due to any cause was observed. The response to the combined regimen and PFS period for each patient was evaluated until at least 2 and a half years after the completion of treatment.

Adverse events (AEs) were graded according to the toxicity criteria of the Japan Clinical Oncology Group,[27] an expanded version of the Common Toxicity Criteria of the National Cancer Institute (version 1.0).

Human antichimeric antibody assay and pharmacokinetics of rituximab

Serum human antichimeric antibody (HACA) levels were monitored at 8 and 10 months after treatment initiation using an enzyme-linked immunosorbent assay (ELISA), as described previously.[28]

Serum rituximab levels were monitored using ELISA for patients who signed another informed consent form to participate in this pharmacokinetic (PK) study. The PK parameters were calculated using WinNonlin PK software (WinNonlin

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Standard Japanese Edition, version 1.1; Scientific Consulting, Apex, NC, USA).

Statistical methods

The ORR, percentage CR, and their 95% confidence intervals (CIs) were calculated with per protocol sets (PPS) of data for all eligible patients and full analysis sets (FAS) of data for all enrolled patients under the F-distribution. The median PFS time, time to CR (TTCR) and time to response (TTR), and their 95% CIs were estimated for all eligible and evaluative patients using the method of Kaplan and Meier, and were compared using the log–rank test. In addition, pretreatment factors affecting the ORR and PFS were analyzed for all eligible and evaluative patients by univariate and multivariate analyses using Fisher's exact test, Wilcoxon's rank sum test, the log–rank test, the logistic regression model or Cox's proportional hazard regression model.

All statistical analyses were performed using SAS software (version 6.12; SAS Institute, Cary, NC, USA). Data used for theses analyses were finally confirmed on March 31, 2004.

Results

Patient characteristics

A total of 69 patients were enrolled from 21 institutions (see Appendix I); 34 patients were allocated to Arm C and 35 patients to Arm S. Patient characteristics at study entry are summarized in Table 1. The median age was 52 years (range, 26–69 years). The major characteristics of the two arms were very similar in both the enrolled and eligible patients. Retrospectively, we analyzed the Follicular Lymphoma International Prognostic Index (FLIPI) in all patients.[29] FLIPI was equally distributed between the two arms. Twenty-eight patients (82%) in Arm C and 30 patients (86%) in Arm S were judged

Table 1. Patient characteristics

Factor	Enrolled (n = 69)			Eligible (n = 66)		
	Arm C	Arm S	Total	Arm C	Arm S	Total
Sex						
Female	18	18	36	17	18	35
Male	16	17	33	15	16	31
Age (years)						
Median	53	50	52	54.5	49.5	52.5
Range	36–65	26–69	26–69	36–65	26–69	26–69
Performance status (ECOG)						
0	29	30	59	28	29	57
1	5	5	10	4	5	9
Histopathology (REAL)†						
Follicular, grade 1	12	11	23	11	11	22
Follicular, grade 2	21	19	40	20	19	39
Follicular, grade 3	0	2	2	0	2	2
Marginal zone B-cell	1	0	1	1	0	1
Low grade B-NHL, NOS‡	0	2	2	0	2	2
No specimen submitted§	0	1	1	0	0	0
Clinical stage (Ann Arbor)						
III	14	15	29	13	14	27
IV	20	20	40	19	20	39
B-symptoms						
Absent	30	33	63	29	32	61
Present	4	2	6	3	2	5
LDH						
Normal	32	31	63	31	30	61
Elevated	2	4	6	1	4	5
No. of extranodal sites						
0–1	25	26	51	24	25	49
≤2	9	9	18	8	9	17
International Prognostic Index						
Low	21	21	42	21	20	41
Low-intermediate	12	12	24	10	12	22
High-intermediate	1	1	2	1	1	2
High	0	1	1	0	1	1
Follicular Lymphoma International Prognostic Index						
Low	16	15	31	16	15	31
Intermediate	12	15	27	10	14	25
High	6	5	11	5	5	10

†According to the diagnosis by the central pathology review. ‡Low-grade B-cell non-Hodgkin lymphoma (NHL) not otherwise specified. §Specimen was not submitted to the central pathology review. LDH, lactic dehydrogenase.

Table 2. Response to therapy

Arm		*n*	No. of patients achieving response						Response rate (95% CI)	
			CR	CRu	PR	SD	PD	NE	%CR	ORR
Arm C	Eligible	32	19 21 30	2	9	1	0	1	66% (47–81%)	94% (79–99%)
	Enrolled	34	21 23 33	2	10	1	0	0	68% (50–83%)	97% (85–100%)
Arm S	Eligible	34	22 23 33	1	10	0	0	1	68% (50–83%)	97% (85–100%)
	Enrolled	35	21 23 33	1	10	0	0	2	66% (44–81%)	94% (81–99%)

Response to each therapy was evaluated according to the International Workshop Criteria for Non-Hodgkin's Lymphoma. CI, confidence interval; CR, complete response; CRu, complete response/unconfirmed; NE, not evaluative due to insufficient follow-up; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

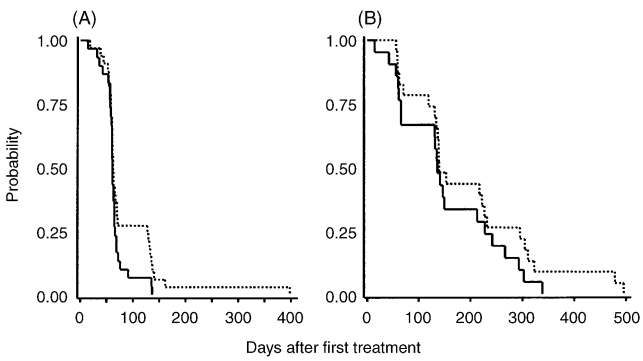

Fig. 1. (A) Time to response (TTR) and (B) time to complete response (TTCR). Medians were estimated by the Kaplan-Meier method. A total of 63 patients (Arm C [-], 30; Arm S [---], 33) were analyzed for TTR, and 44 patients (Arm C, 21; Arm S, 23) for TTCR with per protocol sets of data. Median TTRs in Arm C and Arm S were 61 days (95% confidence interval [CI] 59 to 65 days) and 62 days (95% CI 60–70 days), respectively. The 75th percentile TTRs in Arm C and Arm S were 66 days (95% CI 63 to 76 days) and 140 days (95% CI 66–135 days), respectively ($P = 0.0994$, log–rank test). Median TTCRs in Arm C and Arm S were 136 days (95% CI 65 to 213 days) and 140 days (95% CI 134–227 days), respectively. The 75th percentile TTCRs in Arm C and Arm S were 228 days (95% CI 141 to 293 days) and 295 days (95% CI 153–323 days), respectively ($P = 0.2201$, log–rank test).

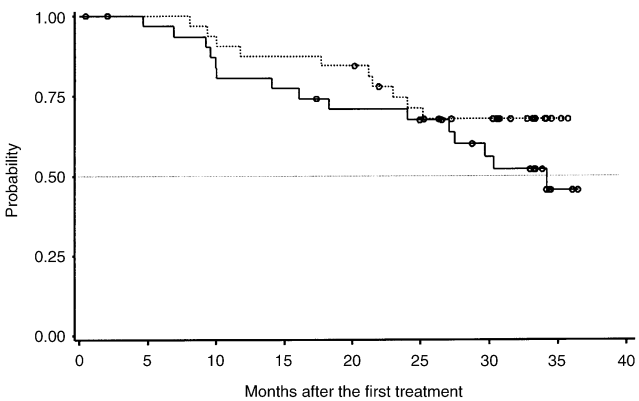

Fig. 2. Progression-free survival (PFS). Medians were estimated by the Kaplan-Meier method. The upper limit of the 95% confidence interval (CI) for Arm C has not yet been determined. A total of 65 patients (Arm C, 32; Arm S, 33) were analyzed with per protocol sets of data. The median PFS time for patients in Arm C (-) was 34.2 months (95%CI, 27.1 months, inestimable), whereas that for patients in Arm S (...) had not yet been reached, with a median follow-up time of 28.2 months. Log–rank test, $P = 0.220$. (o) Censored.

to belong to the low, or low-intermediate risk group categorized by FLIPI. Three patients were judged ineligible by an extramural review committee, because two of them had concomitant active cancer and one had a history of prior chemotherapy, including doxorubicin for the treatment of breast cancer. Sixty-five patients (94%) were confirmed to have FL in the central pathology review.

Response to treatment and survival

Sixty-six eligible patients (Arm C, 32 patients; Arm S, 34 patients) were evaluated with PPSs of data, and 69 patients (Arm C, 34 patients; Arm S, 35 patients) with FASs of data. One patient allocated to Arm C could not be evaluated for response because the first cycle of chemotherapy given was not CHOP (doxorubicin in the CHOP regimen was erroneously replaced with daunorubicin). Two patients (one patient eligible and one ineligible) allocated to Arm S could not be evaluated because they had withdrawn from the study before starting treatment.

As shown in Table 2, similar results of the ORRs and the percentage CRs were obtained in Arm C and Arm S. The ORRs and percentage CRs calculated with PPSs and FASs were similar. Kaplan-Meier curves of TTR and TTCR were plotted for eligible and evaluative patients in each arm, as shown in Fig. 1. Although the median TTRs for patients in Arm C and Arm S were not different (61 days *versus* 62 days, respectively), the 75th percentile TTRs for patients were shorter in Arm C (66 days) than Arm S (127 days), with no statistical difference ($P = 0.0994$, log–rank test). The median TTCRs were similar in Arm C and Arm S (136 days and 140 days, respectively). As shown in Fig. 2, the median PFS time for patients in Arm C ($n = 32$) was 34.2 months

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Table 3. Hematological toxicity

Toxicity	Arm	*n*	Grade 0–2	Grade 3	Grade 4
Any hematological toxicity	Arm C	34	2 (6%)	3 (9%) 32 (94%)	29 (85%)
	Arm S	33	0 (0%)	10 (30%) 33 (100%)	23 (70%)
Leukopenia	Arm C	34	5 (15%)	16 (47%) 29 (85%)	13 (38%)
	Arm S	33	3 (9%)	23 (70%) 30 (91%)	7 (21%)
Neutropenia	Arm C	34	2 (6%)	3 (9%) 32 (94%)	29 (85%)
	Arm S	33	1 (3%)	9 (27%) 32 (97%)	23 (70%)
Thrombocytopenia	Arm C	34	32 (94%)	1 (3%) 2 (6%)	1 (3%)
	Arm S	33	33 (100%)	0 (0%) 0 (0%)	0 (0%)
Anemia	Arm C	34	31 (91%)	3 (9%)	–
	Arm S	33	31 (94%)	2 (6%)	–

Hematological toxicity was evaluated according to the JCOG Toxicity Criteria, an expanded version of the NCI-CTC version 1.0. All hematological toxicities (possibly related to rituximab, or unknown relationship to rituximab) observed during the treatment and follow-up period (for 6 months after the last cycle of CHOP for Arm C, and for 4 months after the last rituximab infusion for Arm S) are listed.

(95%CI, 27.1 months – inestimable), whereas that for patients in Arm S ($n = 33$) had not yet been reached, with a median follow-up time of 28.2 months. One patient (#38) in Arm S died of tumor progression 730 days after the first treatment. No other patients died within approximately 3 years of observation.

Adverse events

Information about AEs was available for 67 patients (Arm C, 34 patients; Arm S, 33 patients) who received protocol treatment. Hematological toxicity was documented at its highest grade throughout the study period. As shown in Table 3, major hematological toxicity was neutropenia; grade 3 or greater neutropenia was observed in 32 patients (94%) in Arm C and in 33 patients (100%) in Arm S; grade 4 neutropenia was seen in 29 patients (85%) in Arm C and in 23 patients (70%) in Arm S. All hematological toxicities were controllable and reversible, although some patients required hematopoietic cytokines.

Grade 3 or greater non-hematological AEs observed during treatment and initial follow-up periods are listed in Table 4. A total of 11 patients (Arm C, seven patients, 21%; Arm S, four patients, 12%) developed 14 events of grade 3 or greater non-hematological adverse events. All non-hematological toxicities were reversible. There was no therapy-related death.

Prognostic factors

Pretreatment factors affecting ORR and PFS were analyzed. Because the sample size of each arm was small, analyses were not performed separately for the two arms, but results were pooled ($n = 64$). There were two factors affecting ORR when analyzed by the Wilcoxon's rank sum test. Patients with PS 0 (41CR, 13PR, 1NC, 0 PD) demonstrated a superior response to those with PS 1 (3CR, 6PR, 0NC, 0PD) ($P = 0.0182$, Wilcoxon's rank-sum). Patients with a tumor size <5 cm (32CR, 6PR, 1NC, 0 PD) had a superior response to those with tumors equal to 5 cm (12CR, 13PR, 0NC, 0 PD) ($P = 0.0066$, Wilcoxon's rank-sum).

However, no factor significantly affected PFS. Multivariate analyses were also performed using the same factors, excluding IPI. There was no factor that independently affected ORR and PFS.

HACA and pharmacokinetics of rituximab

Out of 67 patients who received rituximab, HACA assays were performed for 65 patients (Arm C, 33; Arm S, 32) at 8 months after treatment, and for 64 patients (Arm C, 33; Arm S, 31) at 10 months after treatment. No patient developed HACA. For all 27 patients (Arm C, 14; Arm S 13) who received four rituximab infusions and whose planned monitoring of

Table 4. Grade 3 or greater-non-hematological adverse events

Arm	Patient	Serious adverse event†	Grade‡	Onset timing	Relating drug (causative)
Arm C	#04	Hyperglycemia	3	6th cycle (day 4)	CHOP (diabetes)
(*n* = 32)	#07	Hyperglycemia	3	4th cycle (day 2)	CHOP, rituximab
	#13	Hypertension	3	1st cycle (day 3)	CHOP, rituximab
	#21	Total bilirubin elevation	3	2nd cycle (day 5)	– (constitutional)
	#23	Abdominal pain	3	1st cycle (day 9)	CHOP, rituximab
	#58	Acute cholangitis with elevated AST and ALT	3	3rd cycle (day 10)	CHOP, rituximab
	#59	Hyperglycemia, hypertension	3	5th cycle (day 6)	CHOP, rituximab
Arm S	#25	Total bilirubin elevation	3	6th cycle (day 132)	– (constitutional)
(*n* = 33)	#56	Diarrhea	4	1st cycle (day 13)	– (alimentary)
		Febrile neutropenia	3	3rd cycle (day 12)	CHOP
		Interstitial pneumonia	3	3rd cycle (day 15)	CHOP
	#62	Total bilirubin elevation	3	4th cycle (day 7)	CHOP
	#69	AST and ALT elevation	3	1st cycle (day 10)	CHOP
				2nd cycle (day 8)	CHOP
				6th cycle (day 29)	CHOP

†Grade 3 or greater adverse events other than hematological toxicities that were observed during the treatment and follow-up period (for 6 months after the last cycle of CHOP for Arm C, and for 4 months after the last rituximab infusion for Arm S). ‡JCOG Toxicity Criteria, an expanded version of the NCI-CTC, version 1.0.

Table 5. Pharmacokinetic parameters of rituximab

Arm		Dose (mg/day)	AUC (μg. h/mL)	Cmax† (μg/mL)	$T_{1/2}$ (h)	Clearance‡ (litter/h)	MRT (h)	Vd (litter)
Arm C	Mean	593.9	372 498.9	262.5	232.3	0.0259	335.1	4.49
(*n* = 14)	SD	51.1	111 660.4	73.2	113.8	0.0301	164.2	0.66
Arm S	Mean	596.4	418 901.3	433.5	356.9	0.0128	514.9	5.57
(*n* = 13)	SD	82.6	107 002.6	134.9	163.4	0.0077	235.9	1.95

†Actual measured value. ‡Calculated under the one-compartment model. Time points for serum collection were as follows; Arm C: before, and 10 min and 2 days after each rituximab infusion, and 1 week, 1, 4 and 6 months after the sixth rituximab infusion. Arm S: before, 10 min after each rituximab infusion and 2 days, 1 and 2 weeks, and 1 and 4 months after the sixth rituximab infusion. AUC, area under the curve; Cmax, maximum concentration; $T_{1/2}$, elimination half-life; MRT, mean residence time; Vd, volume of distribution.

serum rituximab levels were completed, pharmacokinetic parameters were calculated throughout the four infusions. As shown in Table 5, Arm S showed higher values for the parameters of area under the curve (AUC), maximum concentration (Cmax), elimination half-life (T1/2), mean residence time (MRT), and volume of distribution (Vd).

Discussion

In this randomized phase II trial, we have demonstrated that the combined use of rituximab and CHOP yielded an ORR of 94% and 97%, and a percentage CR of 66% and 68% in the concurrent arm and the sequential arm, respectively. These ORRs and percentage CRs are superior to those reported for combination chemotherapy regimens containing anthracycline without rituximab, which were conducted after stringent clinical staging with CT. The percentage CR obtained by six to eight cycles of CHOP chemotherapy in untreated patients ($n = 83$) with FL was reported to be 36% (90%CI, 27–46%).[30] The ORR and percentage CR of CHOP chemotherapy obtained by Kimby *et al*. in their randomized study comparing chlorambucil plus prednisone *versus* CHOP in symptomatic low-grade NHL ($n = 127$), were 60% and 18%, respectively.[31]

Data of the present study was comparable to the preceding study on CHOP combined with rituximab in patients with indolent B-NHL regarding efficacy and tolerability. Although the precise schedule of the administration of rituximab in the first phase II study of R-CHOP reported by Czuczman *et al*. was not the same as that of the present study, the concept of concurrent use is identical between their trial and Arm C in the present study.[14] However, the percentage CR of Arm C is less than that of Czuczman *et al*.'s trial, and the median PFS of Arm C appears to be shorter in the present study, although more than 82% of all enrolled patients in our study were in the low or low-intermediate risk group by FLIPI. In Czuczman *et al*.'s trial, as the last two infusions of rituximab were administered 1 month after the sixth CHOP cycle, like in our sequential arm, the design of Czuczman *et al*.'s trial had characteristics of both the concurrent arm and the sequential arm. So it is possible that the higher percentage CR and longer PFS in Czuczman *et al*.'s trial compared to our concurrent arm were partly due to the mixed design of the administration schedule of rituximab, in addition to the possible selection bias in phase II studies.

The South-west Oncology Group (SWOG) in the USA studied six cycles of CHOP followed by four weekly infusions of rituximab in newly diagnosed patients with FL at advanced stages (31% with bulky disease and 30% with B-symptoms). Sixteen (19%) of the 84 evaluative patients had an improved tumor response after rituximab treatment, with an ORR of 72%, including 54% with a CR or CRu. The PFS was 76% at the median follow-up of 2.7 years.[32] The PFS data of the sequential arm in our trial is similar to that of the SWOG trial.

Cancer and Leukemia Group B (CALGB) conducted a randomized phase II study to explore a more suitable administration schedule of rituximab with fludarabine in previously untreated chronic lymphocytic leukemia (CLL) patients.[33] Patients randomly received either six monthly courses of fludarabine concurrently with rituximab followed 2 months later by four weekly doses of rituximab for consolidation therapy, or fludarabine alone followed 2 months later by rituximab consolidation therapy. The ORR with the concurrent regimen was 90% compared to 77% with the sequential regimen. With a median follow-up time of 23 months, the number of relapsed patients was 18 (35%) in the concurrent regimen and 15 (28%) in the sequential regimen. Although PFS and survival appeared to be somewhat longer with the sequential treatment, CALGB concluded that the concurrent use of rituximab and fludarabine was superior. Our randomized phase II study for indolent B-cell NHLs showed similar percentage ORRs and percentage CRs between the two arms, and a seemingly longer PFS in the sequential arm. Because patients in the concurrent arm in the CALGB study received consolidated administration of rituximab after induction therapy, the concurrent arm in the CALGB study had characteristics of the concurrent arm and sequential arm of our present study.

In a randomized phase III study that compared eight cycles of R-CVP to CVP for previously untreated patients with advanced FL, a significantly prolonged TTP of R-CVP was reported (median 32 months *versus* 15 months for CVP; $P < 0.0001$).[18] The median TTP of R-CVP was similar to the median PFS of Arm C in our study. As the toxicity is stronger in CHOP than CVP, it is worthwhile to conduct a randomized phase III trial to compare R-CHOP to R-CVP.

The maintenance use of rituximab after first-line rituximab therapy was also reported to prolong PFS or event-free survival (EFS).[34,35] Future trials to explore the role of maintenance use of rituximab after first-line rituximab containing chemotherapy like Arm C are warranted.

About 25% of patients in Arm S did not achieve a response (PR or higher) before the initiation of rituximab treatment, despite the completion of six cycles of CHOP. In Arm C, more than 90% of patients showed a response after the six cycles of CHOP plus rituximab. The same tendency was also shown in the TTCR, as shown in Fig. 1B. The TTCR of each patient in Arm C was relatively shorter than that in Arm S.

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While grade 3 or greater non-hematological AEs were observed in 11 patients (Arm C, seven patients, 21%; Arm S, four patients, 13%), both arms were well tolerated. Two patients were withdrawn from the study before completion of the planned treatment by AE. One patient in Arm C developed acute cholangitis after the third cycle of CHOP plus rituximab. The other patient in Arm S developed interstitial pneumonia after the third cycle of CHOP. Both patients fully recovered. Hematological toxicities were observed in all treated patients; grade 4 neutropenia was frequent and was observed in 85% of patients in Arm C and in 70% in Arm S. However, these hematological toxicities were manageable with or without supportive care using hematopoietic growth factor. No patient was withdrawn from the study due to hematological toxicity. Grade 3 or greater thrombocytopenia was rare in Arm C and absent in Arm S. Although hematological and non-hematological toxicities were slightly more frequent in Arm C, toxicities were clinically acceptable in both arms.

In conclusion, CHOP combined with rituximab was highly effective in untreated patients with indolent B-NHL, especially FL, either in a concurrent or sequential combination, with acceptable toxicities. Although the time to achieve a response was more rapid with the concurrent combination than the sequential combination, PFS appeared to be slightly longer with the sequential combination, although the difference was not statistically significant. We conclude that both combination schedules deserve further investigation. Considering the promising results of rituximab maintenance therapy reported by other investigators, it would be worthwhile to conduct future trials to establish the role of rituximab maintenance after concurrent and sequential combinations of rituximab plus CHOP therapy.

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Appendix

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