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A phase II Japanese trial of fludarabine, cyclophosphamide and rituximab for previously untreated chronic lymphocytic leukemia

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Abstract

Objective: Fludarabine, cyclophosphamide and rituximab (FCR) is the standard regimen for fit patients with untreated CD20-positive chronic lymphocytic leukemia (CLL). However, this combination is unavailable in Japan because rituximab is not approved for CLL. We investigated the efficacy and safety of FCR in this single-arm, multicenter study designed as a bridging study to the CLL8 study by the German CLL Study Group.

Methods: The study enrolled previously untreated patients with CLL of Binet stage B or C with active disease. Patients with a Cumulative Illness Rating Scale score of $\leq$6 and creatinine clearance of $\geq$70 ml/min were eligible. Patients received 6 cycles of FCR every 28 days and were followed for up to 1 year.

Results: Seven patients were enrolled. The best overall response rate according to the 1996 NCI-WG Guidelines, the primary endpoint of the study, was 71.4% (95% confidence interval, 29.0–96.3%), with one patient achieving complete response. No deaths or progression occurred during follow-up. The main adverse event was hematotoxicity. CD4-positive T-cell count decreased in all patients; most patients showed no reduction in serum immunoglobulin G.

Conclusion: Although the number of patients was limited, FCR appears to be effective with manageable toxicity for treatment-naïve fit Japanese patients with CD20-positive CLL.

Clinical trial number: JapicCTI-132285.

Key words: rituximab, chronic lymphocytic leukemia, phase II clinical trial, FCR

Introduction

Chronic lymphocytic leukemia (CLL) is a rare subtype of leukemia in Japan, accounting for 1–2% of all Japanese lymphoid neoplasm cases (1). In patients with CLL, treatment is typically initiated when the patient has evidence of active disease (2) and initial treatment is selected based on the comorbidity (fitness) and/or chronological age of patients (2). The combination of fludarabine, cyclophosphamide and rituximab (FCR) has been the standard treatment option for previously untreated patients with CLL who are young and fit. In the CLL8 study, a pivotal phase III trial, the German CLL Study Group compared FCR to combination therapy with fludarabine and cyclophosphamide (FC) in treatment-naïve CLL patients who were scored up to 6 on the Cumulative Illness Rating Scale (CIRS) and who had creatinine clearance ≥70 ml/min. The results showed extension of progression-free survival (PFS; median duration: 51.8 months [95% confidence interval (CI), 46.2–57.6] vs. 32.8 months [95% CI, 29.6–36.0], $P < 0.0001$) (3) in the FCR arm with an improved response rate (90 vs. 80%, $P < 0.0001$) and complete response (CR) rate (44 vs. 22%, $P < 0.001$). Notably, overall survival was significantly longer in the FCR arm (median duration: not reached vs. 86.0 months, $P = 0.001$) (4). Additionally, in long-term follow-up for a phase 2 study of the FCR regimen at MD Anderson Cancer Center, about half of patients with a mutated immunoglobulin heavy chain variable gene achieved PFS at 12.8 years and a plateau was seen on the PFS curve (5). However, FCR has not been utilized in Japan because rituximab for CLL has not yet been approved there. We thus conducted a clinical study to confirm the efficacy and safety of rituximab in Japanese patients with untreated CLL in accordance with the study design for the CLL8 study.

Patients and methods

Study design and patients

This study was a prospective, open-label, single-arm, multicenter phase II trial, based on the study design for the CLL8 trial (3), and was conducted at six institutions in Japan.

As in the CLL8 trial, patients received FCR therapy every 28 days for up to six cycles (rituximab 375 mg/m^2 on Day 1 of Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2–6; fludarabine 25 mg/m^2/day and cyclophosphamide 250 mg/m^2/day for the first 3 days of each cycle). Before each cycle of rituximab infusion, patients were premedicated with 50–100 mg oral diphenhydramine hydrochloride, 1000 mg oral acetaminophen and 100 mg intravenous prednisolone. Before Cycle 1, 0.2 mg/kg/day rasburicase was administered to prevent tumor lysis syndrome. From Cycle 2 onward, administration of an antihyperuricemic was recommended. Response to treatment was assessed at the completion of Cycle 3 and 1, 3 and 6 months after final rituximab administration, in accordance with the response criteria stipulated in the 1996 NCI-WG Guidelines (6). Response rates were calculated based on the best response data. After completion of Cycle 3, further treatment was continued at the discretion of the investigator in patients who had achieved a CR or partial response (PR) assessment and in those with stable disease (SD). The patients were followed for up to 1 year after initial rituximab administration. In the protocol, feasibility was evaluated by the rate of grade ≥3 adverse events or adverse drug reactions. Adverse events and adverse drug reactions were coded using the Japanese version of the ICH Medical Dictionary for Regulatory Activities (MedDRA/J) and were then tabulated by preferred terms. Adverse event severity was assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Japanese translation by JCOG (Japan Clinical Oncology Group), 20 November 2012) (7).

The main criteria for discontinuation included: postponing rituximab administration for 4 weeks or longer due to hematologic toxicity of grade 3 or 4; fludarabine or cyclophosphamide dose reduction of more than 50% due to hematologic toxicity; creatinine clearance <30 ml/min and difficulty in continuing treatment due to serious adverse events.

Trimethoprim–sulfamethoxazole prophylaxis for pneumocystis infections and acyclovir prophylaxis for varicella zoster virus reactivation were recommended in the study.

Before the study was initiated, the approval was obtained from the institutional review board at each study center. Each patient provided written informed consent before enrolment. The study was conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice guidelines, and other relevant guidelines, and was registered in the database of the Japan Pharmaceutical Information Center—Clinical Trials Information (JapicCTI-132285).

Patient eligibility

The main inclusion criteria were as follows: treatment-naïve patients who had been diagnosed with CLL according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (8) were at least 20 years of age; were at Binet stage B or C (6), with confirmed active disease based primarily on iwCLL criteria; and had Eastern Cooperative Oncology Group performance status of 0 or 1 (9). The main exclusion criteria were autoimmune cytopenia or Coombs-positive hemolytic anemia, CIRS (10–13) score >6, creatinine clearance no more than 70 ml/min, total bilirubin level exceeding 2.0× the upper limit of normal, and positive for hepatitis B virus surface antigen, hepatitis B surface antibody, hepatitis B core antibody, antibody to hepatitis C virus or antibody to human immunodeficiency virus.

Pharmacokinetics and pharmacodynamics

Serum concentration of rituximab was measured 30 min before administration and 10 min after administration in each cycle and 1, 2, 3 and 6 months after final administration. Anti-rituximab antibody was measured at baseline and 6 months after final administration or at study discontinuation. Serum concentrations of both rituximab and anti-rituximab antibody were measured by enzyme-linked immunosorbent assay. Peripheral CD19-positive cells were counted by flow cytometry at baseline, before administration in each cycle, and 1, 2, 3 and 6 months after final administration.

Statistical analysis

The primary endpoint was the best overall response rate (ORR) at 1 year. Secondary endpoints were overall CR rate, PFS at 1 year and overall survival (OS) at 1 year. PFS was defined as the duration from the day rituximab treatment was initiated to progression or death from all causes. OS was defined as the duration from the day rituximab treatment was initiated to death from any cause. Sample size was set to six patients based on feasibility of enrollment, given the limited number of patients with CLL in Japan. Statistical hypothesis testing was not performed. PFS rate and OS rate were calculated by the Kaplan–Meier method. SAS software version 9.2 (SAS Institute Inc., NC) was used for all analyses.

Table 1. Summarized clinical characteristics of seven patients with CLL

Clinical characteristics	No. of patients (%)
Male/female	5 (71.4%)/2 (28.6%)
Age, years, median (range)	54.0 (48–72)
Age (years)	
≥65 years	2 (28.6%)
≥70 years	1 (14.3%)
ECOG PS 0	4 (57.1%)
Binet stage	
B	2 (28.6%)
C	5 (71.4%)
Presence of B symptoms	2 (28.6%)
Presence of hepatomegaly	0 (0.0%)
Presence of splenomegaly	1 (14.3%)
Time from diagnosis to enrollment, months, median (range)	18 (5–90)
CIRS scores, median (range)	3 (1–6)
Cytogenetic abnormalities	
del(11q)	0 (0.0%)
del(13q)	1 (14.3%)
del(17p)	0 (0.0%)
Trisomy 12	2 (28.6%)
t(11;14)	0 (0.0%)
ZAP-70 expression[a]	1 (14.3%)

ECOG, Eastern Cooperative Oncology Group performance status scale; CIRS, Cumulative Illness Rating Scale; ZAP, zeta-chain-associated protein kinase

[a]ZAP-70 gene expression ≥20%.

Results

Patient disposition and baseline characteristics

This study enrolled seven treatment-naïve patients with CLL (5 men and 2 women) between November 2013 and May 2017. Median age was 54 years (range 48–72 years). Five patients had Binet stage C disease (71.4%) and two had stage B (28.6%). The median time from diagnosis to enrollment was 18 months (range 5–90 months). One patient (14.3%) had chromosome 13q-deletion [del(13q)] and two (28.6%) had trisomy 12. Patients with del(11q), del(17p) or t(11;14) translocation were not enrolled. Patient characteristics are shown in Table 1.

All seven enrolled patients had at least one cycle of protocol treatment. On average, patients received five treatment cycles (range 1–6). Two patients discontinued study treatment due to adverse events. One patient was unable to receive the full dose of 375 mg/m^2 due to sinus node dysfunction that appeared during rituximab administration at Cycle 1. The other was discontinued because the fifth treatment cycle was postponed by more than 4 weeks due to grade 4 leukopenia. Both of these patients subsequently improved or recovered from the adverse events that led to discontinuation of the study. During the median follow-up period of 324 days (range 39–374 days), no deaths occurred.

Efficacy endpoints

The best ORR at 1 year after starting FCR was 71.4% (5/7: 95% CI, 29.0–96.3%). The CR rate was 14.3% (1/7: 95% CI, 0.4–57.9%) and the PR rate was 57.1% (4/7: 95% CI, 18.4–90.1%). The remaining two patients discontinued treatment due to adverse events. In one of these patients, target lesions met the criteria of CR: lymphadenopathy resolved and the absolute lymphocyte count decreased from 86 165/μl to below the normal range, but the patient was assessed as SD because of low platelet count and hemoglobin level at 1 year after starting treatment. The other patient was withdrawn from the study due to sinus node dysfunction during Cycle 1 of treatment and was not evaluable for efficacy. Five patients that responded to therapy had the best response 6 months after the final treatment with rituximab. The best response and response rate are shown in Table 2.

Since no deaths or CLL progression occurred during the study period, the 1-year PFS rate and 1-year OS rate were 100%.

Safety analysis

Safety analysis was performed in the seven patients who received protocol treatment. Adverse events of any grade developed in all seven patients (Table 3). Events of high frequency included nausea (6 patients, 85.7%), leukopenia (6 patients, 85.7%), neutropenia (6 patients, 85.7%), CD4 lymphopenia (6 patients, 85.7%), thrombocytopenia (6 patients, 85.7%), lymphocytopenia (5 patients, 71.4%) and anemia (5 patients, 71.4%). Six patients received granulocyte colony-stimulating factor with a median number of cycles of 4 (range 0–6) during FCR. Infections developed in three patients (42.9%: nasopharyngitis in 2 patients and pharyngitis in 1 patient). These infections were all grade 2 or lower. All patients received pneumocystis infection prophylaxis with trimethoprim–sulfamethoxazole and six patients (85.7%) received varicella zoster virus reactivation prophylaxis with acyclovir. Febrile neutropenia of grade 3 occurred in one patient (14.3%). Three patients developed infusion-related reactions (IRRs), including grade 3 in 1 patient (hypoxia). In the patient who developed hypoxia, rituximab infusion was interrupted for 90 min at Cycle 1; the patient recovered with corticosteroids and oxygen inhalation therapy. This patient developed grade 2 or lower IRRs (fever, edema, rash and pruritus) during each infusion until Cycle 5. Other patients had IRRs only with the first infusion.

A serious adverse event developed in one patient (grade 2 sinus node dysfunction) but improved with supportive therapy. Non-hematological adverse events of grade 3 or higher developed in two patients (grade 3 febrile neutropenia in 1 patient, grade 3 hypoxia in 1 patient), but both patients recovered. No adverse events were noted that resulted in death or a second malignancy. The study treatment was discontinued in two patients due to adverse events (sinus node dysfunction in 1 patient and neutropenia in 1 patient).

As a result of hematological toxicity of grade 3 or above, rituximab administration in Cycle 2 or later was postponed by 7 days or more in four patients (57.1%). The doses of fludarabine and cyclophosphamide were reduced in two patients (28.6%); no patients required dose reduction of rituximab.

Immunosuppression

CD4-positive cells and serum immunoglobulin G (IgG) were measured in seven patients who underwent protocol treatment. CD4-positive cells decreased after treatment initiation in all patients. CD4-positive cell counts were 3276.0 ± 2380.2/μl at baseline, 525.0 ± 586.2/μl at Week 4, 208.0 ± 133.0/μl at Week 8, 120.3 ± 54.2/μl at Week 12 and 189.2 ± 84.3/μl at 12 months after treatment initiation. CD4-positive cell counts decreased after treatment initiation and remained decreased after 12 months. Changes in CD4 counts are shown in Fig. 1. Serum IgG remained at

Table 2. Response to therapy

n	No. of patients achieving response					Response rate (95% CI)	
	CR	PR	SD	PD	NE	%ORR	%CRR
7	1	4	1	0	1	71.4% (29.0–96.3%)	14.3% (0.4–57.9%)

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; CRR, complete response rate.

Table 3. Incidence of adverse events

SOC and preferred term	All grades (%)[a]	Grade 3/4
Gastrointestinal disorders		
Nausea	6 (85.7%)	0 (0%)
Constipation	4 (57.1%)	0 (0%)
Vomiting	3 (42.9%)	0 (0%)
General disorders and administration site conditions		
Pyrexia	3 (42.9%)	0 (0%)
Infections and infestations		
Nasopharyngitis	2 (28.6%)	0 (0%)
Blood and lymphatic system disorders		
Febrile neutropenia	1 (14.3%)	1 (14.3%)
Anemia	1 (14.3%)	1 (14.3%)
Vascular disorders		
Hypertension	2 (28.6%)	0 (0%)
Hypotension	2 (28.6%)	0 (0%)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	2 (28.6%)	1 (14.3%)
Psychiatric disorders		
Insomnia	2 (28.6%)	0(0%)
Skin and subcutaneous tissue disorders		
Rash maculopapular	2 (28.6%)	0 (0%)
Pruritus	2 (28.6%)	0 (0%)
Investigations	7 (100.0%)	6 (85.7%)
Neutrophil count decreased	6 (85.7%)	6 (85.7%)
White blood cell count decreased	6 (85.7%)	6 (85.7%)
CD4 lymphocytes decreased	6 (85.7%)	6 (85.7%)
Platelet count decreased	6 (85.7%)	2 (28.6%)
Lymphocyte count decreased	5 (71.4%)	5 (71.4%)
Hemoglobin decreased	5 (71.4%)	2 (28.6%)
Red blood cell count decreased	3 (42.9%)	0 (0%)
Alanine aminotransferase increased	2 (28.6%)	0 (0%)
Weight decreased	2 (28.6%)	0 (0%)

SOC, system organ class.

[a]Adverse events of all grades that occurred in two or more patients, or adverse events of grade 3–4.

the same level after treatment initiation for all patients except those who had high IgG before treatment initiation. No opportunistic infections occurred during the study period.

Pharmacokinetics

Serum concentration of rituximab was measured in the seven patients who received protocol treatment. Mean serum concentration of rituximab in the five patients who received six cycles of treatment (71%) was 328 000 ng/ml, which was also the highest mean value at Cycle 5 (Fig. 2). The maximum serum concentration was at least 300 000 ng/ml in four patients and <300 000 ng/ml in one patient. No differences were noted between men and women. The pharmacokinetic parameters (clearance, volume of distribution and mean residence time) were estimated with one-compartment model analysis as the rituximab concentration–time curve of the individual patient was found to fit this model. Serum concentrations of rituximab are shown in Fig. 2, the pharmacokinetic parameters [area under the curve (AUC) and trough serum concentration (C_{trough})] per cycle are shown in Table 4 and the pharmacokinetic parameters are shown in Table 5.

Anti-rituximab antibodies

Anti-rituximab antibodies in serum were measured at baseline, and 6 months after the final dose of rituximab or at study discontinuation, in the seven patients who received treatment. All patients tested negative.

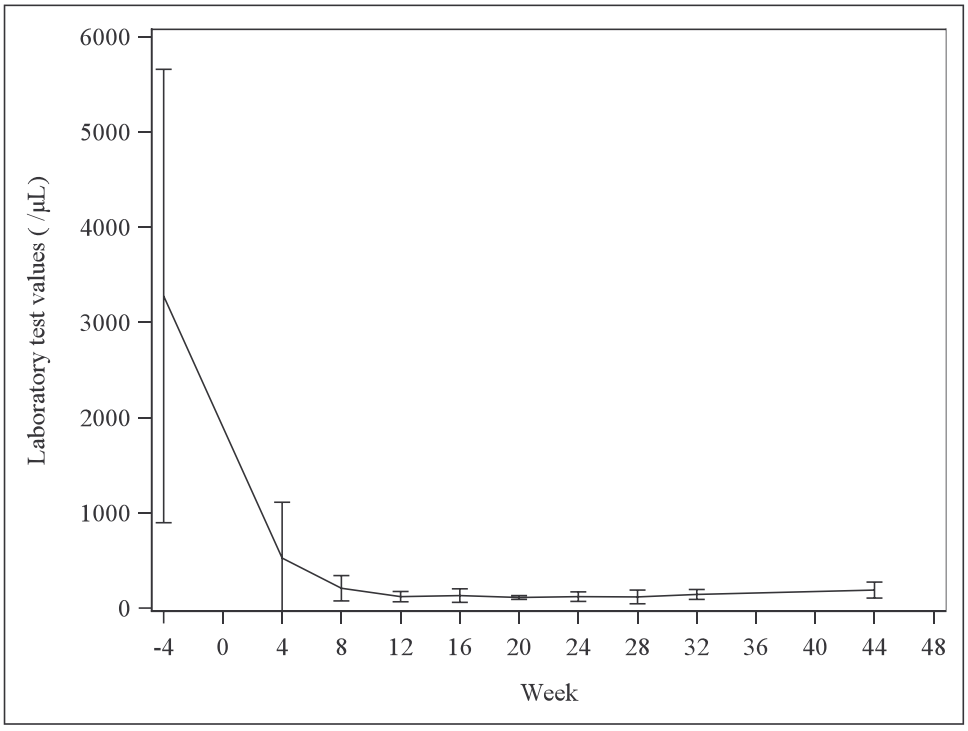

Figure 1. Changes in mean CD4 count ($n = 7$).

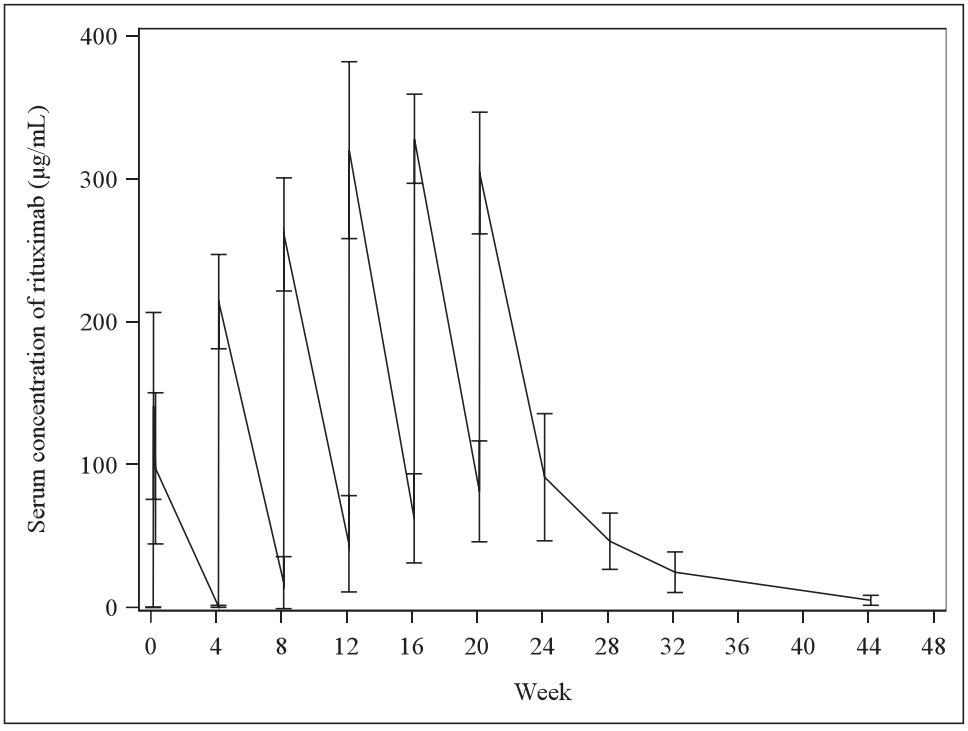

Figure 2. Serum concentration of rituximab. Mean ± SD serum concentration of rituximab in patients who received six cycles of treatment ($n = 5$).

Table 4. Median C_{trough} and AUC of rituximab per cycle

	Our study		Li J et al. (16)	
Cycle	C_{trough}, μg/ml Median	AUC, μg/ml·d Median	C_{trough}, μg/ml Median	AUC, μg/ml·d Median
1	1.12	1690	Responder: 2.3 Non-responders: 1.1	Responder: 786 Non-responders: 638
2	16.5	3420	–	–
3	45.4	4810	Responder: 26.9 Non-responders: 13.8	Responder: 2894 Non-responders: 1626
4	67.8	6620	–	–
5	70.6	6310	–	–
6	80.7	6440	Responder: 105 Non-responders:58.9	Responder: 4505 Non-responders: 3147

AUC, area under the curve.

Table 5. Mean ± SD for pharmacokinetic parameters of rituximab in patients who received six cycles of treatment

n	C_{max}, μg/ml	AUC_{0-t}, mg/ml·h	CL, ml/h	V, l	MRT, h	$T_{1/2}$, h
5	351 ± 36.3	804 ± 155	100 ± 127	3.37 ± 0.883	349 ± 342	242 ± 237

C_{max}, maximum concentration; CL, clearance; V, volume; l, liter; MRT, mean residence time; $T_{1/2}$, elimination half-life.

Discussion

This phase II study was designed as a bridging study to the CLL8 study, a pivotal phase III study that evaluated efficacy of the FCR regimen compared with FC in untreated fit patients with CLL. The number of patients included in the study was small, which limits the definitive conclusions that can be drawn from the study data. However, no new safety signals for FCR were detected in these Japanese CLL patients, and the efficacy findings were in line with those from the CLL8 study.

In this study, a serious adverse event occurred in one patient and non-hematological adverse events of grade 3 or higher in two patients. However, these patients improved or recovered, so the events were considered manageable. No new safety signals for FCR were detected in Japanese CLL patients in this study. IRRs can be a major complication of rituximab; such reactions were observed in three patients in this study, but they were manageable in all cases. These findings suggest that FCR is feasible in this patient population and that rituximab infusion is tolerable in the setting of treatment-naïve CLL.

Although lymphocytopenia and decreased CD4-positive cell count were not recognized as adverse events in the CLL8 study (3, 4), because the study protocol defined that grade 4 lymphocytopenia were not captured as laboratory abnormality (3), FCR is associated with profound and sometimes prolonged lymphocytopenia and decreased CD4-positive cell count (14, 15), placing the patients at risk of opportunistic infections. Our study also showed a reduction in the number of CD4-positive cells after FCR. However, no infections of grade 3 or higher were observed, and there were no instances of opportunistic infection, possibly because prophylaxis for pneumocystis pneumonia was recommended in the protocol and was administered to all patients. Serum IgG level was not reduced in most patients.

Treatment-naïve Japanese patients with CLL who were treated with FCR achieved a best ORR of 71.4% (95% CI: 29.0–96.3%) among the seven patients. Although the ORR of the present study is numerically lower than that of the FCR of the CLL8 study (90%, 95% CI: 87–93%) (3), the present study was underpowered to detect difference in response rates due to small sample size, and early discontinuation of study treatment in two patients also had large impact on response rate. In one of these patients, target lesions met the criteria of CR but the patient was assessed as having SD because the patient did not meet the criteria of bone marrow recovery according to the iwCLL criteria (8). Therefore, we assessed that the response achieved in the present study was in line with the results of the CLL8 study.

Rituximab displayed time-dependent pharmacokinetics with wide interpatient variability in the study. The rituximab serum concentration in this study was compared with that of the REACH study in which relapsed CLL patients were treated with FCR (16) with the same dose and schedule of rituximab, since pharmacokinetics were not evaluated in the CLL8 study (3). Median C_{trough} at Cycle 1, Cycle 3 and Cycle 6 in the study was similar to those of the rituximab in the study of relapsed chronic lymphocytic leukemia (REACH) study. The AUC of this study was higher than that of the REACH study presumably due to wide sampling intervals in this study (Table 4). Other pharmacokinetics parameters could not be compared due to using different compartment model. Based on these data, we believe that the same dose and schedule of rituximab used in the FCR regimen in the CLL8 and REACH studies are adequate for Japanese CLL patients.

This study has limitations for evaluating the efficacy and safety of FCR therapy in Japanese patients, mainly due to the small number of patients enrolled and also because the follow-up time was too short to evaluate the durability of response. However, given the low incidence of CLL in the Japanese population, we believe that our results represent the best available data on efficacy and safety of FCR in Japanese CLL patients. Recently, the role of chemoimmunotherapy for CLL has been challenged by the introduction of novel agents. The study that compared FCR versus ibrutinib–rituximab in patients 70 years or younger with untreated CLL resulted in superior PFS and OS in the ibrutinib–rituximab arm (17). As a result, regimens that include novel agents including ibrutinib rather than FCR are

considered to be preferred first-line therapy in young and fit patients in the current guidelines (18). However, the role of the FCR regimen for untreated CLL remains for a specific population with a mutated immunoglobulin heavy chain variable region status (18, 19) in which FCR have been shown to achieve long-term durable remission suggestive of cure (5). Time-limited treatment with known long-term results like FCR may be preferred especially in younger patients.

In conclusion, although the number of patients was limited, FCR was feasible with manageable toxicity for treatment-naïve fit Japanese patients with CD20-positive CLL, and the efficacy was in line with that seen in the CLL8 study.

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Conflict of interest statement

Dr Koji Izutsu reports grants from Zenyaku, during the conduct of the study; grants and personal fees from Chugai, grants and personal fees from Celgene, grants and personal fees from Eisai, grants and personal fees from Novartis, grants and personal fees from AbbVie, grants and personal fees from Janssen, grants and personal fees from Kyowa Kirin, grants and personal fees from Takeda, grants and personal fees from AstraZeneca, personal fees from FUJIFILM Toyama Chemical, grants and personal fees from Ono, grants and personal fees from MSD, personal fees from Nihon Mediphysics, personal fees from Dainihon Sumitomo, grants and personal fees from Bayer, grants and personal fees from HUYA Japan, personal fees from Bristol Myers Squib, personal fees from Mundipharma, personal fees from Asahi Kasei Pharma, personal fees from Astellas, personal fees from Otsuka, grants and personal fees from Daiichi Sankyo, grants from ARIAD, grants from Astellas Amgen, grants from Sanofi, grants from Symbio, grants from Solasia, grants from Zenyaku, grants from Pfizer, grants and personal fees from BeiGene, grants from Incyte and grants from Yakult, outside the submitted work. Dr Tomohiro Kinoshita reports grants from Zenyaku, during the conduct of the study; grants and personal fees from Takeda, grants and personal fees from Chugai, grants and personal fees from Ono, grants from MSD, grants from Eisai, grants from Gilead, grants from Soleisia, outside the submitted work. Dr Jun Takizawa reports grants and personal fees from Chugai, grants and personal fees from Kyowa Kirin, grants from Sanofi, grants and personal fees from Astrazeneca, personal fees from AbbVie, grants and personal fees from Ono, grants and personal fees from Eisai, grants and personal fees from Nippon Shinyaku, grants and personal fees from Sumitomo Dainippon, personal fees from Celgene, grants and personal fees from Mochida, grants and personal fees from Daiichi Sankyo, grants and personal fees from Takeda, personal fees from Janssen, grants and personal fees from MSD and grants from Astellas, outside the submitted work. Dr Suguru Fukuhara reports grants and personal fees from Zenyaku, during the conduct of the study. Dr Go Yamamoto has nothing to disclose. Dr Yasuo Ohashi reports personal fees from Chugai, personal fees from Daiichi-Sankyo and personal fees from Sanofi, outside the submitted work. Dr Junji Suzumiya reports grants and personal fees from Chugai, grants from Kyowa-Kirin, grants from Shin-Nihon Kagaku, grants from Astellas, grants and personal fees from Eisai, grants and personal fees from Takeda, grants and personal fees from Celgene, personal fees from Janssen, personal fees from Bristol Myers Squibb, personal fees from AbbVie and personal fees from AstraZeneca, outside the submitted work. Dr Kensei Tobinai reports personal fees from Zenyaku Kogyo, during the conduct of the study; grants and personal fees from Eisai, grants and personal fees from Takeda, grants and personal fees from Mundipharma, personal fees from HUYA Bioscience International, grants and personal fees from Kyowa Kirin, grants and personal fees from Celgene, grants and personal fees from Chugai Pharma, grants and personal fees from Ono Pharmaceutical, personal fees from Yakult, personal fees from Daiichi Sankyo, personal fees from Bristol-Myers Squibb, personal fees from Meiji Seika Kaisha, personal fees from Solasia Pharma, personal fees from Verastem, grants from Janssen and grants from AbbVie, outside the submitted work.

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