International Journal of Hematology (2021) 114:217–221
https://doi.org/10.1007/s12185-021-03151-5

ORIGINAL ARTICLE

Pretreatment levels of serum soluble interleukin-2 receptor are useful in selecting the treatment regimen for newly diagnosed advanced-stage follicular lymphoma with low tumor burden

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Received: 1 February 2021 / Revised: 7 April 2021 / Accepted: 7 April 2021 / Published online: 13 April 2021

Abstract

High pre-treatment serum soluble interleukin-2 receptor (sIL-2R) levels are associated with poor overall survival (OS) of patients with newly diagnosed follicular lymphoma (FL). We evaluated the usefulness of pre-treatment sIL-2R levels in selecting a treatment regimen for advanced-stage FL with low tumor burden (FL-LTB). This retrospective, multicenter observational study enrolled consecutive patients who received a rituximab-containing regimen for newly diagnosed advanced stage FL-LTB (grade 1–3a) between 2008 and 2018. We applied a previously reported cut-off value of 1800 IU/mL for sIL-2R. A total of 211 patients were eligible for the analysis. Among patients with high sIL-2R (47 patients, 22.3%), the OS rates for patients treated by rituximab monotherapy (R-mono) (11 patients) were significantly lower than those treated by rituximab-combination chemotherapy (R-chemo) (36 patients): 5-year OS rates were 66.7% and 94.4%, respectively ($P=0.007$). Among patients with low sIL-2R (164 patients, 77.7%), OS rates were comparably good between the R-mono group (34 patients) and the R-chemo group (130 patients): 5-year OS rates were 100% and 98.3%, respectively ($P=0.38$). Our results suggest that R-chemo may yield better OS than R-mono for patients with newly diagnosed advanced-stage FL-LTB and high pre-treatment serum sIL-2R levels.

Keywords SIL-2R levels · Advanced stage FL · LTB FL

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Introduction

Recently, we reported that high pretreatment levels of serum soluble interleukin-2 receptor (sIL-2R) are correlated with poor overall survival (OS) of patients with newly diagnosed follicular lymphoma (FL) who required immediate treatment [1]. For asymptomatic patients with advanced-stage FL with low tumor burden (LTB) (FL-LTB), watchful waiting remains the appropriate approach; whereas, rituximab monotherapy (R-mono) has been suggested as a good alternative [2]. However, in terms of improving OS, the optimal treatment strategy for advanced stage FL-LTB is still controversial. Moreover, whether rituximab in combination with chemotherapy (R-chemo) improves OS of selected patients has not been well investigated. In addition, an easily measurable pretreatment prognostic biomarker for patients with advanced-stage FL-LTB is urgently needed. Therefore, we aimed to evaluate the usefulness of pretreatment sIL-2R levels in selecting treatment regimens for these patients.

Methods and patients

We retrospectively analyzed all patients with newly diagnosed FL in our 12 institutions between January 1, 2008, and December 31, 2018. Inclusion criteria were age of 18 years or older and first-line treatment with rituximab-containing regimen. Exclusion criteria were grade 3b FL, and histologic transformation (HT) at the first diagnosis, managed with watchful waiting as an initial strategy or treated without rituximab.

Serum sIL-2R levels were routinely measured, at the physician's discretion, using either chemiluminescent enzyme immunoassay (CLEIA) or sandwich enzyme-linked immunosorbent assay (ELISA). The pretreatment sIL-2R levels were selected from the sIL-2R levels measured closest to the date of the diagnostic biopsy sampling (within 6 months before and after sampling). We determined tumor burden according to the Groupe d' Etude des Lymphomes Folliculaires (GELF) criteria [3]. We retrospectively collected data from our institutions' electronic medical records, in cooperation with the relevant physicians responsible for the patients. We checked the patient's reference in each institution, with every other institution to complete the datasheet and avoid including the same patient twice.

The primary outcome was OS, defined as the time from the initial diagnosis to death from any cause, or the last follow-up. The date of the biopsy that originated the final FL diagnosis was considered the time of initial diagnosis. We analyzed OS according to the Kaplan–Meier method and compared differences between subgroups using a log-rank test. The association between OS and the treatment regimen was evaluated using univariate and multivariate Cox proportional hazards model analyses. We also calculated crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). In multivariable models with OS, we adjusted the values for FL international prognostic index (FLIPI), as FLIPI is the most commonly used prognostic index for OS with pretreatment information. We applied a previously published cutoff value of 1800 IU/mL for sIL-2R [1]. EZR (Jichi Medical University, v. 2.51) was used to perform all statistical analyses [4]. Two-sided P values ≤ 0.05 were considered statistically significant. This study was approved by the institutional review board of Osaka University and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. This research study was conducted retrospectively from data obtained for clinical purposes and all the procedures being performed were part of the routine care. In view of the retrospective nature of the study, informed consent was obtained in the form of opt-out on the website.

Results

Totally, 233 patients with newly diagnosed advanced-stage FL-LTB were registered. After excluding 19 patients who were initially managed with watch and wait strategy, 214 patients remained. Then, we excluded three patients who were treated without rituximab. Finally, 211 patients were eligible for this analysis. Patient flowchart is shown in Fig. 1.

Patient characteristics are shown in Table 1. The median age at the time of diagnosis was 63 years (range 30–91 years), and 62.1% of the patients were women. Most patients (167 patients, 79.1%) had grade 1 or 2 histology at the time of diagnosis, and 81 patients (38.4%) had a high FLIPI score. Out of these patients, 45 (21.3%) were treated with R-mono and 166 (78.7%) were treated with R-chemo. The most common R-chemo regimen was R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) for 88 patients (53.0%), followed by R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) for 36 patients (21.7%), BR (rituximab and bendamustine) for 23 patients (13.9%), and R-THP-COP (rituximab, cyclophosphamide, pirarubicin, vincristine, and prednisone) for 19 patients (11.4%). Rituximab maintenance (RM) was performed in 75 patients (35.6%). We registered ten re-biopsy cases (4.7%), including seven with consistent FL histology (3.3%) and three with HT (1.4%).

The median pretreatment sIL-2R levels were 756 IU/mL (range 166–7910 IU/mL). Measurement of sIL-2R was carried out at 52 days before and 99 days after the date of the diagnostic biopsy. The area under the ROC curve was 0.68 (95% CI 0.48–0.88) with a cutoff value of 1870 IU/mL for sIL-2R (sensitivity 0.80; specificity 0.60).

The median follow-up duration was 5.3 years (range 0.1–11.4 years). The FLIPI score was significantly higher in patients with high sIL-2R (47 patients, 22.3%) than in patients with low sIL-2R (164 patients, 77.7%); high FLIPI

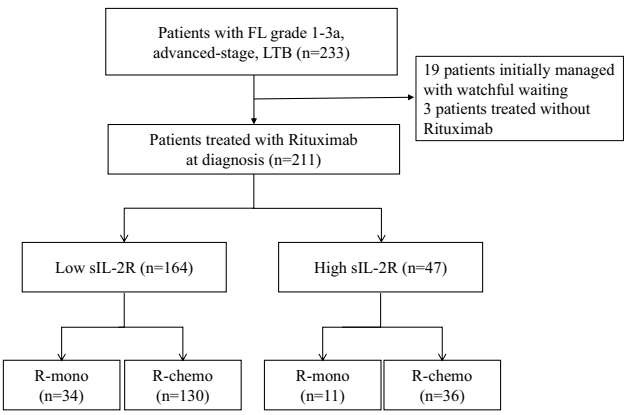

Fig. 1 Overview of patient selection flow

Table 1 Patient characteristics

Factor	All patients $n=211$		Missing		Low sIL-2R				*P* value	High sIL-2R				*P* value
					R-mono $n=34$		R-chemo $n=130$			R-mono n=11		R-chemo $n=36$		
	n	%	*n*	%	*n*	%	*n*	%		*n*	%	*n*	%	
Women	131	62.1	0	0	18	52.9	83	63.8	0.322	8	72.7	22	61.1	0.722
Age > 60 years	117	55.5	0	0	20	58.8	61	46.9	0.25	7	63.6	29	80.6	0.256
Bone marrow invasion	76	36	13	6.2	8	23.5	43	33.1	0.398	7	63.6	18	50	0.48
B symptoms	4	1.9	6	2.8	2	5.9	1	0.8	0.122	0	0	1	2.8	1
Tumor size ≧ 6 cm	5	2.4	7	3.3	1	2.9	3	2.3	1	0	0	1	2.8	1
FLIPI			3	1.4					0.474					0.599
Low	49	23.2	–	–	11	32.4	35	26.9		1	9.1	2	5.6	
Intermediate	78	37	–	–	16	47.1	52	40		3	27.3	7	19.4	
High	81	38.4	–	–	7	20.6	40	30.8		7	63.6	27	75	
FLIPI-2			134	63.5					0.276					0.631
Low	42	19.9	–	–	11	32.4	30	23.1		0	0	1	2.8	
Intermediate	20	9.5	–	–	1	2.9	13	10		2	18.2	4	11.1	
High	15	7.1	–	–	2	5.9	5	3.8		1	9.1	7	19.4	
Grade			0	0					0.637					1
1 or 2	167	79.1	–	–	30	88.2	101	77.7		9	81.8	27	75	
3, unclassified	13	6.2	–	–	1	2.9	10	7.7		0	0	2	5.6	
3a	21	10	–	–	2	5.9	15	11.5		1	9.1	3	8.3	
Unknown	10	4.7	–	–	1	2.9	4	3.1		1	9.1	4	11.1	
Hb < 12 g/dL	26	12.3	1	0.5	4	11.8	10	7.7	0.493	5	45.5	7	19.4	0.118
LDH ≧ 230 IU/L	48	22.7	0	0	3	8.8	22	16.9	0.295	3	27.3	20	55.6	0.168
N of nodal lesions ≧ 5	92	43.6	2	0.9	7	20.6	54	41.5	0.028	6	54.5	25	69.4	0.472
ECOG-PS ≧ 2	8	3.8	3	1.4	2	5.9	1	0.8	0.113	1	9.1	4	11.1	1
β2MG ≧2 mg/L	34	16.1	130	61.6	3	8.8	17	13.1	0.351	4	36.4	10	27.8	1
Rituximab maintenance	75	35.5	0	0	13	38.2	47	36.2	0.843	5	45.5	10	27.8	0.292

scores were 72.3% and 29.2%, respectively ($P<0.001$). RM was equally performed in patients with high sIL-2R (15 patients, 31.9%) and low sIL-2R (60 patients, 36.6%) ($P=0.61$). The OS rates were significantly lower for patients with high sIL-2R than for those with low sIL-2R; 5-year OS rates were 88.3% and 98.7%, respectively ($P=0.01$) (Fig. 2).

Among the patients with high sIL-2R, there was no significant difference in the patient backgrounds between R-mono (11 patients, 23.4%) and R-chemo (36 patients, 76.6%) groups; high FLIPI scores were 63.6% and 75.0% ($P=0.47$), respectively, followed by RM in 45.5% and 27.8% ($P=0.29$), respectively. However, the OS rates for patients treated with R-mono were significantly lower than for those treated with R-chemo; 5-year OS rates were 66.7% and 94.4%, respectively ($P=0.007$) (Fig. 3a).

Contrarily, among the patients with low sIL-2R, the OS rates were not significantly different between the groups; 5-year OS rates were 100% for the R-mono group and 98.3% for the R-chemo group ($P=0.38$) (Fig. 3b). There was also no significant difference in the following patient backgrounds between the R-mono (34 patients, 20.7%) and

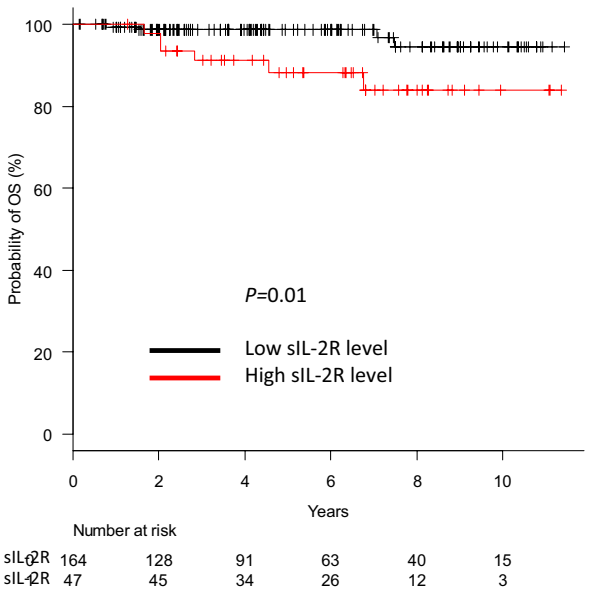

Fig. 2 OS by pre-treatment sIL-2R levels of patients with newly diagnosed advanced stage FL-LTB. Patients with high pretreatment sIL-2R levels showed significantly lower OS

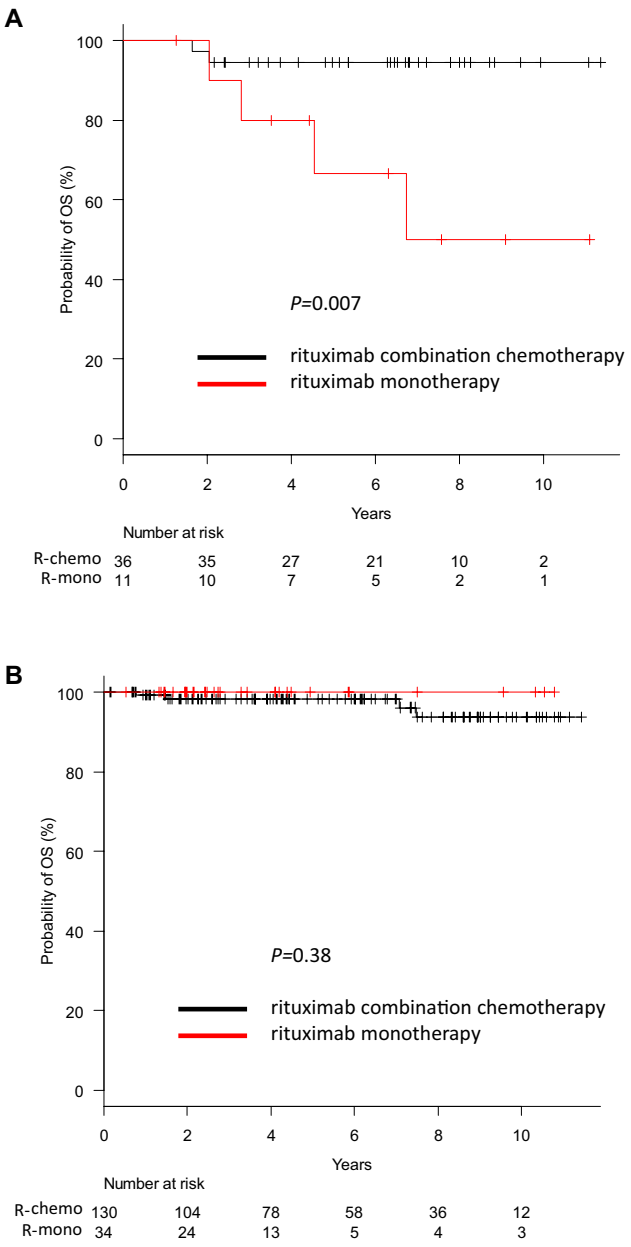

Fig. 3 **a** OS by rituximab-containing regimen in patients with high sIL-2R levels. Patients treated with rituximab combination chemotherapy showed a significantly better OS. **b** OS by rituximab-containing regimen in patients with low sIL-2R levels. There was no difference in OS between the two treatments. OS, overall survival; sIL-2R, soluble interleukin-2 receptor; LTB, low tumor burden; FL, follicular lymphoma

R-chemo (130 patients, 79.3%) groups; high FLIPI scores were 20.6% and 31.5% ($P=0.29$), followed by RM in 38.2% and 36.2% of the patients ($P=0.84$), respectively.

In univariate Cox proportional hazards model analysis for patients with high sIL-2R levels, the crude HR of R-mono was 7.41 (95% CI 1.35–40.5, $P=0.02$). In multivariate analysis of these patients, we demonstrated that R-mono was independently associated with poor OS (HR 7.77, 95% CI 1.42–42.6, $P=0.018$). High FLIPI score showed an HR of 2.41, 95% CI 0.28–20.9, $P=0.42$ (Table 2).

Discussion

Our study is the first to show a statistically significant prognostic impact of pretreatment sIL-2R levels on OS in patients with newly diagnosed advanced-stage FL-LTB. Furthermore, this is the first study to show that R-chemo, and not R-mono is significantly associated with better OS among patients with high pretreatment sIL-2R levels. We also demonstrated equally good OS for patients with low sIL-2R levels who received R-mono or R-chemo.

Serum sIL-2R levels can be measured easily and quickly in a clinical setting; therefore, we suggest that it may be a useful biomarker for selecting treatment regimens for patients with advanced-stage FL-LTB. Our results show that it may be better to treat patients with LTB and high pretreatment sIL-2R with a similar strategy adapted for patients with high tumor burden. Since it is difficult to set OS as a primary endpoint of prospective trials of patients with FL, retrospective study provides useful information regarding the OS of these patients.

In our study, patients initially managed with watchful waiting were excluded because we often monitor sIL-2R levels as well as symptoms to determine the optimal timing of treatment in clinical practice. Instead, we focused on patients who required immediate treatment at diagnosis to compare R-mono and R-chemo as the initial treatment. Therefore, our results cannot be applied to judge whether to watch or initiate treatment for patients with high sIL-2R levels at diagnosis.

This study has some limitations. First, this was a retrospective study and the pretreatment sIL-2R levels were not measured at the predetermined timing. The time between

Table 2 Univariate and multivariate analyses of prognostic factors associated with OS

Factor	Group	Univariate			Multivariate		
		Hazard ratio	95%CI	*P* value	Hazard ratio	95%CI	*P* value
Regimen	R-chemo	Reference			Reference		
	R-mono	7.41	1.35–40.49	0.021	7.77	1.42–42.63	0.018
FLIPI	Low/intermediate	Reference			Reference		
	High	2.09	0.24–17.92	0.503	2.41	0.28–20.93	0.424

sIL-2R measurement and treatment initiation was different between patients. Therefore, we adopted only sIL-2R levels measured during 6 months before and after the date of the diagnostic biopsy to restrict the time of measurement. Second, sIL-2R levels were not all measured using the same method. However, the reference ranges for the CLEIA and ELISA were almost the same. This suggested highly compatible test values for both the methods. Third, since sIL-2R levels may be influenced by many conditions, we could not determine whether the elevated sIL-2R levels exclusively represent the lymphoma activity. Additionally, there may be unmeasured confounding factors which influenced the association between sIL-2R levels and outcomes. Among the factors we collected, there was no statistical difference between R-chemo group and R-mono group (Table 1). However, it may result from small number of patients. We may find some factors that are statistically different between the groups with much larger populations. In this study population of high sIL-2R, the risk of R-mono regimen was independent factor of high FLIPI score (Table 2). Since FLIPI consists of age, hemoglobin, lactate dehydorogenase, stage, number of nodal areas involved, this result suggested these were not confounding factors. Lastly, no uniform process was used to select the treatment regimen. Accordingly, further studies, including prospective trials, will be needed to confirm these associations.

In conclusion, our results suggest that for patients with newly diagnosed advanced-stage FL-LTB who had high sIL-2R levels and received immediate treatment at diagnosis, R-chemo may bring better OS than R-mono, whereas both regimens showed equally good OS for patients with low sIL-2R levels.

Acknowledgements The authors would like to thank all participants of this study for their contribution. We also thank our colleagues from Osaka University Center of Medical Data Science and Advanced Clinical Epidemiology Investigator's Research Project for providing valuable insight and expertise for our research.

Declarations

Conflict of interest Our study group received research funding from Eisai Co. Kenji Nozaki received personal fees from Chugai and Celgene outside the submitted work. Satoru Kosugi received personal fees from Novartis, Bristol-Myers Squibb, Eisai, Takeda, Kyowa Kirin, Chugai, Ono, Nippon Shinyaku, Janssen, Celgene, and Pfizer outside the submitted work. Hirohiko Shibayama received Grants and personal fees from Eisai during the conduct of the study; Grants and personal fees from Takeda, Ono, Sumitomo Dainippon Pharma, Mundi Pharma, and Nippon Shinyaku; Grants from Teijin, MSD, Shionogi, and Taiho; personal fees from Novartis, Janssen, Celgene, Chugai, Kyowa Kirin, Otsuka, AstraZeneca, Avvie, Daiichi Sankyo, Fujimoto, Sanofi, Bristol-Meyers Squibb and Pfizer outside the submitted work.

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