Prognostic value of the soluble interleukin-2 receptor level after patients with follicular lymphoma achieve a response to R-CHOP

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ABSTRACT

Objectives: Follicular lymphoma (FL) is a clinically and biologically heterogeneous disease. Therefore, it is important to identify factors that can predict its clinical outcome.

Methods: We retrospectively evaluated the usefulness of soluble interleukin-2 receptor (sIL-2R) levels after R-CHOP (posttreatment sIL-2R) in 72 patients with newly diagnosed FL who had either a complete response (CR) or partial response. With the use of a recursive partitioning analysis, we determined the cut-off values of post- and pretreatment sIL-2R levels that were associated with disease progression, which corresponded to 486.5 and 5405 U/mL, respectively.

Results: The high posttreatment sIL-2R group showed a significantly inferior progression-free survival (PFS) compared to the low posttreatment sIL-2R group in all patients (3-year PFS 52.6% vs. 77.4%, \( P = 0.003 \)), and in patients with CR (3-year PFS 57.1% vs. 82.1%, \( P = 0.034 \)). Although a multivariate analysis showed that pretreatment sIL-2R, but not posttreatment sIL-2R, was an independently significant predictive factor for disease progression, among patients with low pretreatment sIL-2R levels, those with high posttreatment sIL-2R levels tended to have inferior PFS. There was a significant trend in PFS among the high pretreatment sIL-2R group, the low pre- and high posttreatment sIL-2R group, and the low pre- and low posttreatment sIL-2R group (\( P < 0.001 \)).

Conclusion: Among patients with a low pretreatment sIL-2R level who exhibited a positive response to R-CHOP, the posttreatment sIL-2R level may help to identify those with a poor prognosis.

KEYWORDS

Follicular lymphoma; soluble interleukin-2 receptor; R-CHOP; posttreatment; pretreatment; recursive partitioning analysis; rpart; prognostic factor

Introduction

Follicular lymphoma (FL) is the most common form of indolent lymphoma. It is a clinically and biologically heterogeneous disease [1,2]. The prognosis of patients with FL has dramatically improved in the rituximab era [3]. However, although 70% of patients with FL achieve a complete response (CR) after first-line immunochemotherapy [4], approximately 20% of patients relapse within 2 years [5]. There are various treatment options for FL, ranging from observation to stem cell transplantation. The clinical course of FL varies widely, and thus optimal treatment strategies have not yet been established. Therefore, the identification of prognostic factors is important for the selection of suitable treatments.

The follicular lymphoma international prognostic index (FLIPI) [6] and FLIPI 2 [7], both of which focus only on clinical factors, are the most widely used prognostic factors for FL. Recently, m7-FLIPI, which includes the mutation status of seven genes, has been reported to be a new model of clinicogenetic risk; the analysis of genetic mutations leads to a more accurate prognosis in FL [2]. However, in routine practice, it would be difficult to evaluate genetic mutations in FL.

The interleukin-2 receptor (IL-2R) is expressed on the cell membrane and induces mononuclear cell activation [8,9]. In past reports, an elevated serum soluble interleukin-2 receptor (sIL-2R) level at diagnosis was associated with poor outcomes in some lymphomas, including FL [10–13]. However, there have been few reports on the significance of sIL-2R after first-line treatment. In diffuse large B cell lymphoma, elevated sIL-2R levels after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) were correlated with early relapse [14], but the prognostic impact of sIL-2R levels after R-CHOP has not yet been analyzed in FL. Therefore, the aim of this retrospective study was to determine whether sIL-2R levels after first-line treatment with R-CHOP could predict the prognosis in patients with FL who achieved a response.
Methods

Patients

We retrospectively evaluated 72 patients with newly diagnosed FL who had been treated with R-CHOP as first-line treatment from January 2005 to October 2015 at Jichi Medical University Hospital and subsequently had a complete or partial response. The diagnosis of FL was determined according to the World Health Organization (WHO) classification. Patients who underwent stem cell transplantation or radiation as the upfront consolidative treatment, or who did not have data available on sIL-2R at diagnosis or after R-CHOP, were excluded. Patients who were diagnosed as having grade 3b or transformed FL were also excluded, because they are usually treated as for an aggressive lymphoma. Patients were diagnosed as stage I (n = 3), stage II (n = 7), stage III (n = 30), or stage IV (n = 32), respectively. The response was evaluated according to the revised response criteria for malignant lymphoma [15], using 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) in 68 patients and computed tomography in four. The imaging evaluations after treatment were performed by the discretion of the attending physicians, but the posttreatment scanning was usually performed with 6 to 12 months intervals even without any signs of progression. A laboratory analysis of sIL-2R was performed as a routine practice. The standard value of sIL-2R in our facility was below 477 U/mL and the upper normal limit of lactate dehydrogenase was 216 IU/L. This retrospective study was approved by the Bioethics Committee for Epidemiologic Research, Jichi Medical University.

Statistical methods

Recursive partitioning was used to determine the optimal cutoff levels of serum sIL-2R at the diagnosis and after R-CHOP for disease progression. The differences in clinical and laboratory features between groups were compared by Fisher’s exact test and the Mann-Whitney U test. Progression-free survival (PFS) was calculated from the day that the response was evaluated until disease progression, death, or the last evaluation. Overall survival (OS) was measured from the day when the response to R-CHOP treatment was evaluated until death or until the last evaluation. PFS and OS were calculated using the Kaplan-Meier method and compared between two groups using the log-rank test, and among three groups using log-rank trend tests. For a multivariate analysis, a Cox proportional hazards model was used, with a stepwise backward selection of independent variables. The correlation between two variables was calculated using the Pearson correlation coefficient.

All statistical analyses were performed with EZR version 1.30 (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.2.2). More precisely, it is a modified version of R commander (version 2.2–0), which includes statistical functions that are frequently used in biostatistics [16]. The ‘rpart’ package was used for recursive partitioning analyses. All P values less than 0.05 were considered to be statistically significant.

Results

Serum sIL-2R in patients with FL

The sIL-2R levels at diagnosis and after R-CHOP were defined as pre- and posttreatment sIL-2R, respectively. The median levels of pre- and posttreatment sIL-2R were 2,040 U/mL (range, 213–18,600 U/mL) and 389 U/mL (range, 178–1,690 U/mL), respectively.

A Cox proportional hazard analysis showed that patients with a higher logarithm of posttreatment sIL-2R levels (hazard ratio (HR) 4.14, 95% confidence interval (CI), 0.61–27.9, P = 0.144) tended to have an inferior PFS. Therefore, the prognostic value of posttreatment sIL-2R was evaluated by stratifying patients according to their posttreatment sIL-2R levels. With the use of recursive partitioning analysis for disease progression, we determined that the cut-off value for the posttreatment sIL-2R level was 486.5 U/mL (Figure 1); 19 patients (26.4%) had posttreatment sIL-2R levels higher than this cut-off value (Table 1). The pretreatment sIL-2R levels in the high posttreatment sIL-2R group were significantly higher than those in the low posttreatment sIL-2R group.

In this study, 21 patients were diagnosed as CT-PR, including CT-PR and PET negative (n = 6), CT-PR
and PET positive \((n = 13)\), and CT-PR without PET scan \((n = 2)\). The median posttreatment sIL-2R level was 442 U/mL (range, 182–876 U/mL) in patients with CT-PR and PET negative and 437 U/mL (range, 246–670 U/mL) in patients with CT-PR and PET positive, and there was no statistically significant difference \((P = 0.566)\).

### Prognostic value of the posttreatment sIL-2R level

The median follow-up time for the survivors was 4.9 years (range, 0.9–9.5 years). The 3-year PFS and 7-year OS for all of the patients were 70.6% (95% CI = 57.7–80.3%) and 86.1% (95% CI = 67.5–94.5%), respectively. Among the 57 patients who achieved CR after R-CHOP, 3-year PFS and 7-year OS were 75.7% (95% CI = 60.8–85.5%) and 87.3% (95% CI = 64.4–95.9%), respectively.

The 3-year PFS in the high posttreatment sIL-2R group was significantly worse than that in the low posttreatment sIL-2R group (52.6% [95% CI = 28.7–71.9%] vs. 77.4% [95% CI = 61.7–87.3%], \(P = 0.003\)) (Figure 2(A)), and the 7-year OS was only marginally inferior (69.7% [95% CI = 35.2–88.3%] vs. 93.3% [95% CI = 61.3–88.3%), \(P = 0.059\)). A high posttreatment sIL-2R level was a predictive factor for disease progression even when adjusted for FLIPI (HR 3.05, 95% CI = 1.39–6.71, \(P = 0.005\)).

Even in patients with CR, a high posttreatment sIL-2R level correlated with an inferior 3-year PFS (57.1% [95% CI = 28.4–78.0%] vs. 82.1% [95% CI = 64.0–91.6%], \(P = 0.034\)) (Figure 2(B)). There was no difference in the 7-year OS between the high posttreatment sIL-2R group and the low posttreatment sIL-2R group (72.0% [95% CI = 23.8–92.8%] vs. 92.9% [95% CI = 59.1–99.0%], \(P = 0.295\)).

### Prognostic value of the pretreatment sIL-2R level

Since the high posttreatment sIL-2R group had a significantly higher level of pretreatment sIL-2R than the low posttreatment sIL-2R group, the association

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**Figure 2.** Kaplan–Meier estimates of progression-free survival in all patients (A) and in those who achieved CR (B), stratified according to the posttreatment sIL-2R levels.
between the pretreatment sIL-2R level and the clinical outcome was evaluated. Recursive partitioning analysis showed that the cut-off value of the pretreatment sIL-2R level for disease progression was 5,405 U/mL. Thirteen patients (18.1%) had a pretreatment sIL-2R level of \( \geq 5,405 \) U/mL. The high pretreatment sIL-2R group had significantly inferior PFS and OS than the low pretreatment sIL-2R group (3-year PFS 36.9% [95% CI = 12.5–62.0%] vs. 79.0% [95% CI = 65.0–87.8%], respectively, \( P < 0.001 \); and 7-year OS 45.8% [95% CI = 6.1–80.4%] vs. 95.1% [95% CI = 81.6–98.7%], respectively, \( P = 0.002 \)).

Multivariate analyses for prognostic factors

As shown in Table 2, a univariate analysis demonstrated that posttreatment sIL-2R, pretreatment sIL-2R, and treatment response after R-CHOP were significantly associated with PFS (\( P = 0.003 \), \( P < 0.001 \), and \( P = 0.005 \), respectively). In our cohort, 14 of 74 patients received rituximab maintenance, but the maintenance therapy was not significantly associated with PFS in univariate analysis. A multivariate analysis that included the factors with borderline significance (\( P < 0.2 \)) in a univariate analysis revealed that a high pretreatment sIL-2R level and the treatment response were independent prognostic factors for PFS (HR 4.07, 95% CI = 1.68–9.89, \( P = 0.002 \); and HR 3.15, 95% CI = 1.28–7.80, \( P = 0.013 \), respectively), whereas the posttreatment sIL-2R level was not. Among the 59 patients in the low pretreatment sIL-2R group, those with high posttreatment sIL-2R levels had a PFS that was marginally inferior to that in those with low posttreatment sIL-2R levels (3-year PFS 66.7% [95% CI = 28.2–87.8%] vs. 80.9% [95% CI = 65.1–90.1%], respectively, \( P = 0.097 \)). There was a significant trend in PFS among the high pretreatment sIL-2R group, the low pre- and high posttreatment sIL-2R group, and the low pre- and low posttreatment sIL-2R group (\( P < 0.001 \)) (Figure 3).

Reduction of the tumor burden may be important, and therefore we analyzed the impact of \( \log \) clearance, defined as the ratio of logarithmically transformed values of the pre- and posttreatment sIL-2R levels. However, a Cox proportional hazard model showed that a higher \( \log \) clearance of sIL-2R was significantly

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**Table 2. Univariate and multivariate analyses of prognostic factors associated with PFS.**

| Factor               | Group          | \( N \) | 3y-PFS          | Univariate Hazard ratio | Multivariate Hazard ratio |
|----------------------|----------------|--------|-----------------|-------------------------|--------------------------|
|                      |                |        | \( P \) Value   |                         |                          |
| Posttreatment sIL-2R | \(<486.5 \) U/mL | 53     | 0.774 (0.617–0.873) | 0.003                   | 1                        |
|                      | \( \geq 486.5 \) U/mL | 19    | 0.526 (0.287–0.719) | \(<0.001\)               | 1                        |
| Pretreatment sIL-2R  | \(<5405 \) U/mL | 59     | 0.790 (0.650–0.878) | \(1.95\) (0.69–5.49)    | 0.002                    |
| Pretreatment sIL-2R  | \( \geq 5405 \) U/mL | 13    | 0.369 (0.125–0.620) |                         |                          |
| Pretreatment LDH     | \(<ULN\)       | 47     | 0.730 (0.563–0.842) | 0.940                   |                          |
| FLIPI                | low            | 25     | 0.668 (0.443–0.819) |                         |                          |
|                      | high           | 45     | 0.749 (0.581–0.857) |                         |                          |
| Sex                  | Male           | 34     | 0.688 (0.481–0.826) | 0.214                   |                          |
|                      | Female         | 38     | 0.720 (0.540–0.840) |                         |                          |
| ECOG PS              | \(<2\)         | 66     | 0.724 (0.587–0.823) | 0.437                   |                          |
|                      | \( \geq 2\)    | 2      | 0.500 (0.111–0.804) |                         |                          |
| B symptoms           | present        | 9      | 0.667 (0.282–0.878) | 0.582                   |                          |
|                      | not present    | 63     | 0.709 (0.566–0.812) |                         |                          |
| Grade                | 1,2            | 41     | 0.652 (0.474–0.783) | 0.098                   | 1                        |
|                      | 3a             | 24     | 0.795 (0.534–0.919) | 0.58 (0.20–1.65)        |                          |
| Extranodal sites     | \(<1\)         | 32     | 0.718 (0.511–0.849) | 0.438                   |                          |
|                      | \( \geq 1\)    | 40     | 0.771 (0.593–0.879) |                         |                          |
| Therapy maintenance  | no maintenance | 58     | 0.686 (0.544–0.792) |                         |                          |
| Treatment response   | CR             | 57     | 0.757 (0.608–0.855) | 0.005                   | 1                        |
|                      | PR             | 15     | 0.519 (0.245–0.736) |                         |                          |

PFS: progression-free survival, sIL-2R: soluble interleukin-2 receptor, LDH: lactate dehydrogenase, ULN: upper limit of normal, FLIPI: follicular lymphoma international prognostic index, ECOG: Eastern Cooperative Oncology Group, PS: performance status, CR: complete response, PR: partial response.

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**Figure 3.** Kaplan–Meier estimates of progression-free survival in patients stratified according to the pre- and posttreatment sIL-2R levels.
associated with more frequent disease progression (HR 4.13, 95% CI 1.35–12.7, \( P = 0.013 \)). This was probably due to the strong correlation between the log clearance of sIL-2R and the logarithm of pretreatment sIL-2R \(( r = 0.917, P < 0.001 )\). In fact, when adjusted for the logarithm of pretreatment sIL-2R, the log clearance of sIL-2R was not a predictive factor for disease progression (HR 1.08, 95% CI 0.12–9.97, \( P = 0.947 \)).

**Discussion**

This study investigated whether the posttreatment sIL-2R levels were associated with the prognosis in patients with FL who achieved at least a partial response to R-CHOP.

The pretreatment sIL-2R level has been reported to be a prognostic factor in FL, and an elevated sIL-2R level at diagnosis was observed to be associated with disease activity and a poor prognosis [10–13]. A multivariate analysis in our cohort also showed that a high pretreatment sIL-2R level was an independent prognostic factor for disease progression in successfully treated FL.

There have been no previous reports on the prognostic value of the posttreatment sIL-2R level in FL. In this study, we demonstrated that a high posttreatment sIL-2R level was associated with inferior PFS, independent of the FLIPI score. However, in a multivariate analysis that included the pretreatment sIL-2R level as an independent variable, the posttreatment sIL-2R level did not have an independent prognostic significance for PFS. This could be explained by the fact that the posttreatment sIL-2R level was strongly correlated with the pretreatment sIL-2R level. To exclude the influence of the pretreatment sIL-2R level, we evaluated the impact of posttreatment sIL-2R in patients with low pretreatment sIL-2R. High posttreatment sIL-2R levels nearly significantly correlated with an inferior PFS, and therefore the posttreatment sIL-2R level may make it possible to identify high-risk patients among those with a low pretreatment sIL-2R level.

It has been reported that disease progression within 2 years after diagnosis was associated with a high risk of death in patients with FL who received first-line R-CHOP [17]. This study showed that the pretreatment and posttreatment sIL-2R levels may predict early progression. Therefore, novel therapeutic strategies should be considered for patients with a high risk of early progression. Maintenance therapy with rituximab was associated with prolonged PFS in patients who exhibited a response to R-CHOP [18]. In this study, however, although three patients with high posttreatment sIL-2R levels received maintenance therapy, two of them experienced early progression at 1.8 and 3.2 years after R-CHOP. Therefore, the efficacy of rituximab as maintenance therapy in high-risk patients needs further investigation.

This study has several limitations. First, this is a retrospective study and the pre- and posttreatment sIL-2R levels were measured at the discretion of the attending physicians. In fact, the pre- and posttreatment sIL-2R levels were not measured in seven patients during the study period. In addition, the time when the sIL-2R level was measured after the end of treatment was different among patients (median 55 days, range 7–119 days). Second, the sIL-2R level is not a specific marker of lymphoma activity. Elevated sIL-2R levels may partly represent inflammatory and immunological reactions brought about by immunochemistry.

Lastly, this study only evaluated patients who received R-CHOP. Therefore, the role of pre- and posttreatment sIL-2R levels after treatment with novel agents such as lenalidomide, idelalisib, and obinutuzumab should be evaluated in the future.

In conclusion, posttreatment sIL-2R levels could be a useful marker for an inferior prognosis in patients with FL who are successfully treated with R-CHOP, especially in those with low pretreatment sIL-2R levels. Further clinical studies will be needed to identify an optimal therapeutic approach for high-risk patients.

**Disclosure statement**

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