Laboratory of Clinical Pharmacy[1], Gifu Pharmaceutical University, Gifu; Department of Pharmacy[2]; Department of Hematology[3], Gifu Municipal Hospital, Gifu, Japan

# Risk factors for developing infusion reaction after rituximab administration in patients with B-cell non-Hodgkin's lymphoma

T. Tachi[1,2], M. Yasuda[2], K. Usui[1], M. Umeda[2], K. Nagaya[2], T. Osawa[2], A. Ichihashi[2], Y. Noguchi[1], H. Goto[3], S. Kasahara[3], T. Takahashi[3], C. Goto[2], H. Teramachi[1]

*Received April 16, 2015, accepted May 15, 2015*

*Hitomi Teramachi, Laboratory of Clinical Pharmacy, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu-shi, Gifu 501-1196, Japan*
*teramachih@gifu-pu.ac.jp*

*Pharmazie 70: 674–677 (2015)* *doi: 10.1691/ph.2015.5620*

Rituximab (RTX), a monoclonal antibody against CD20, is known to cause fewer side effects than conventional anti-cancer drugs; however, infusion reaction (IR), which is specific to monoclonal antibody therapy, is frequently triggered by RTX. Therefore, we designed this study to identify risk factors based on clinical test values for developing IR after RTX administration. Eighty-nine patients with B-cell non-Hodgkin's lymphoma who had received RTX for the first time between February 2010 and March 2013, at the Gifu Municipal Hospital were enrolled as subjects. Analysis of data was conducted for 87 patients, after excluding patients whose data were missing. Univariate analysis showed significant differences in the number of patients exhibiting a soluble interleukin-2 receptor (sIL-2R) level > 2,000 U/L and hemoglobin (Hb) < lower standard limit (LSL) between the IR and non-IR groups. Multivariate analysis showed significant differences with respect to sIL-2R > 2,000 U/L [odds ratio (OR), 4.463; 95% confidence interval (CI), 1.262-15.779; $P = 0.020$], Hb < LSL [OR, 3.568; 95% CI, 1.071-11.890; $P = 0.038$], and steroid administration [OR, 0.284; 95% CI, 0.094-0.852; $P = 0.025$]. Our findings show that sIL-2R > 2,000 U/L, Hb < LSL, and a lack of steroid premedication are risk factors for developing IR following RTX treatment.

## 1. Introduction

Rituximab (RTX), a chimeric murine/human anti-CD20 monoclonal antibody, has shown a 40% response rate against CD20 positive B-cell non-Hodgkin's lymphoma as a single dose treatment (Press et al. 2001). The therapeutic efficacy of RTX can be enhanced by combining it with CHOP chemotherapy (R-CHOP) (Coiffier et al. 2002). Drugs such as RTX that specifically target a single protein are generally considered to cause fewer side effects than conventional anti-cancer drugs; however, they occasionally trigger an infusion reaction (IR), a side effect specific to monoclonal antibody therapy. It has been reported that IR often occurs between 30 and 120 min after the administration of such drugs (Maloney et al. 1997; Winkler et al. 1999), causing severe symptoms in approximately 10% of patients and death in some rare cases. However, in many cases, patients recover after adequate intervention (Plosker and Figgitt 2003). IR occurs far more frequently during the first administration of RTX (approximately 77%–80% of cases) (Lenz 2007; Schwartzberg et al. 2008), compared to another monoclonal antibody drug, bevacizumab, for which the incidence of IR is reported to be only 3% (Schwartzberg et al. 2008). The high risk of developing IR after RTX administration makes it important to identify risk factors for this event. Factors such as myelopathic damage (Hong et al. 2013) and tumor mass (Hagberg and Holmbom 2000) have previously been shown to influence the risk of developing IR after RTX administration. However, there have only been a few studies to evaluate the relationship between the development of IR and clinical test values, which are far easier to measure. Yasuda et al. (2014) studied the impact of a soluble interleukin-2 receptor (sIL-2R) level > 2,000 U/L, lactate dehydrogenase (LDH) > 2 × upper standard limit (USL) and hemoglobin (Hb) < lower standard limit (LSL) on changes in body temperature before and after RTX administration. Univariate analysis revealed that sIL-2R, LDH, and Hb were significantly associated with the development of IR.

Therefore, in this study the clinical test values of patients with B-cell non-Hodgkin's lymphoma undergoing initial RTX administration were analyzed by multivariate analysis in order to identify whether clinical test values such as sIL-2R, LDH, and Hb are risk factors for IR development.

## 2. Investigations and results

Among 89 patients who were enrolled as subjects in this study, data from 87 patients were analyzed after excluding patients whose data were missing (Fig. 1). Of the 87 patients, 33 developed IR. The demographic characteristics of all 87 patients are shown in Table 1. The cohort consisted of 54 men and 33 women, with an age range of 67.5 ± 13.3 years. Diffuse large B-cell lymphoma tissue type was found in the majority of patients ($n = 51$), and most patients received R-CHOP ($n = 53$).

The univariate analysis results between the IR and non-IR groups are shown in Table 2. Significant differences were observed between these groups with respect to sIL-2R > 2,000 U/L and Hb < LSL ($P = 0.026$ and $P = 0.019$, respectively), and differ-

**Table 1: Demographic characteristics of the patients**

| | | *n* | Mean ± SD (Median) |
|---|---|---|---|
| Total patients | | 87 | |
| Gender (male/female) | | 54/33 | |
| Age (years) | | | 67.5 ± 13.3 (69.0) |
| Height (cm) | | | 159.3 ± 9.1 (160.6) |
| Weight (kg) | | | 54.6 ± 10.6 (52.6) |
| | | *n* | Rate |
| Diagnosis | Diffuse large B cell lymphoma | 51 | 58.6% |
| | Follicular lymphoma | 13 | 14.9% |
| | Mucosa-Associated Lymphoid Tissue | 11 | 12.6% |
| | Burkitt's lymphoma | 1 | 1.1% |
| | Mantle cell lymphoma | 1 | 1.1% |
| | Lymphoblastic Lymphoma | 1 | 1.1% |
| | B cell lymphoma | 5 | 5.7% |
| | Non-Hodgkin lymphoma | 4 | 4.6% |
| Multiagent regimen | R-CHOP[a)] | 53 | 60.9% |
| | R-THP-COP[b)] | 21 | 24.1% |
| | Rituximab only | 9 | 10.3% |
| | R-COP[c)] | 1 | 1.1% |
| | R + CODAX-M/IVAC[d)] | 1 | 1.1% |
| | R + ETP + PSL[e)] | 1 | 1.1% |
| | R + PSL[f)] | 1 | 1.1% |

a) rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, b) rituximab, cyclophosphamide, tetrahydropyrany adriamycin, vincristine, predonisolone, c) rituximab, cyclophosphamide, vincristine, prednisolone d) rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate, ifosfamide, etoposide, cytarabine, e) rituximab, etoposide, prednisolone, f) rituximab, prednisolone, SD; standard deviation

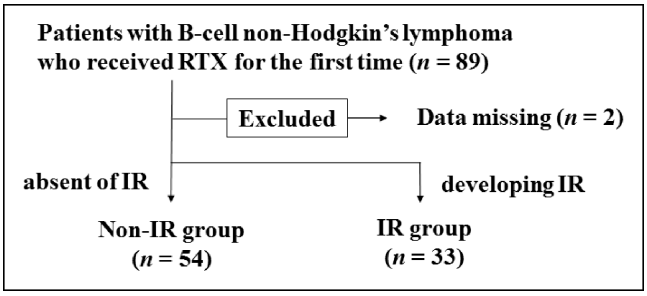


Fig. 1: Summary of patient characteristics in this study cohort, IR, infusion reaction.

ences in BUN > USL and steroid administration had a $P < 0.25$ ($P = 0.238$ and $P = 0.101$, respectively).

Multivariate analysis was performed by setting development of IR as an objective variable for comparison with sIL-2R > 2,000 U/L, Hb < LSL, BUN > USL, and steroid administration, all of which had a $P < 0.25$ in univariate analysis, and LDH > 2 × USL, which was previously identified as a possible predictive factor (Yasuda et al. 2014). The results are shown in Fig. 2. Significant differences in the risk of IR were found for sIL-2R > 2,000 U/L [odds ratio (OR), 4.463; 95% confidence interval (CI), 1.262-15.779; $P = 0.020$], Hb < LSL [OR, 3.568; 95% CI, 1.071-11.890; $P = 0.038$], and steroid administration [OR, 0.284; 95% CI, 0.094-0.852; $P = 0.025$].

**Table 2: Results ofa univariate analysis**

| Item | Condition | Non-IR ($n = 54$) | IR ($n = 33$) | *P* |
|---|---|---|---|---|
| Gender | Male | 22 (40.7%) | 11 (33.3%) | 0.490 |
| Age | ≥ 65 years | 36 (66.7%) | 21 (63.6%) | 0.773 |
| sIL-2R | > 2000 U/L | 15 (27.8%) | 17 (51.5%) | 0.026* |
| LDH | > 2 × USL [422 U/L] | 11 (20.4%) | 7 (21.2%) | 0.925 |
| AST | > USL [33 U/L] | 11 (20.4%) | 10 (30.3%) | 0.293 |
| ALT | > USL [42 U/L (male), 27 U/L (female)] | 11 (20.4%) | 6 (18.2%) | 0.803 |
| ALP | > USL [338 U/L] | 8 (14.8%) | 6 (18.2%) | 0.678 |
| T-BIL | > USL [1.2 mg/dL] | 5 (9.3%) | 3 (9.1%) | 0.979 |
| BUN | > USL [20 mg/dL] | 14 (25.9%) | 5 (15.2%) | 0.238 |
| SCr | > USL [1.0 mg/dL (male), 0.8 mg/dL (female)] | 11 (20.4%) | 5 (15.2%) | 0.542 |
| Hb | < LSL [13.0 g/dL (male), 12.0 g/dL (female)] | 31 (57.4%) | 27 (81.8%) | 0.019* |
| WBC | < LSL [$3.8 \times 10^3/\mu L$] | 9 (16.7%) | 8 (24.2%) | 0.387 |
| PLT | < LSL [$14.0 \times 10^4/\mu L$] | 12 (22.2%) | 9 (27.3%) | 0.593 |
| Steroid | Administrated | 26 (48.1%) | 10 (30.3%) | 0.101 |

IR, infusion reaction; sIL-2R, human soluble interleukin-2 receptor; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; T-BIL, total bilirubin; BUN, blood urea nitrogen; Scr, serum creatinine; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; USL, upper standard limit; LSL, lower standard limit, $^*P < 0.05$

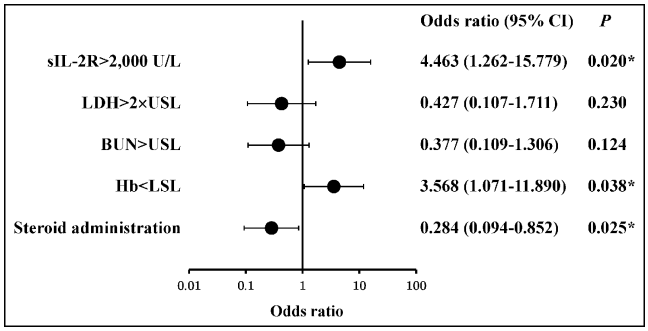


Fig. 2: Results of a multiple logistic regression analysis, sIL-2R, human soluble interleukin-2 receptor; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Hb, hemoglobin; USL, upper standard limit; LSL, lower standard limit, $^{*}P < 0.05$.

## 3. Discussion

Previous studies have found that sIL-2R > 2,000 U/L, LDH > 2 × USL, and Hb < LSL are related to the risk of IR after RTX treatment (Yasuda et al. 2014). LDH is one of the most important categories in the international prognosis index (Park et al. 2014), a leading index evaluating the prognosis of non-Hodgkin's lymphoma, and a lymphoma patient who shows high sIL-2R at the beginning of treatment has a significantly lower remission and 5-year survival rate, as well as a poor prognosis (Goto et al. 2005). In this study, risk factors for developing IR following RTX administration in B-cell non-Hodgkin's lymphoma patients were found to be sIL-2R > 2,000 U/L and Hb < LSL, both of which are easy to measure in routine clinical practice. We also found that steroid administration reduced the risk of developing IR. However, neither LDH > 2 × USL nor any of the other categories were found to be significantly associated with the risk of IR. In addition to forming part of the international prognosis index, LDH is strongly associated with clinical tumor status. Although LDH > 2 × USL was previously shown to be related to the development of IR (Yasuda et al. 2014), this was not replicated in our study. In the clinical setting, there is a tendency to administer steroids to patients with high LDH levels prior to treatment; it is therefore possible that an increase in body temperature was suppressed in these patients, which in turn reduced the risk of IR. However, by using multivariate analysis in this study, the confounding factors caused by steroid administration were adjusted. The mechanism by which RTX treatment leads to IR has not been completely elucidated; however, previous studies have indicated that it may involve the release of cytokines such as TNF-α and IL-6, which trigger temporary inflammation and allergic reactions (Lenz 2007; Winkler et al. 1999). Cytokines are therefore likely to be important factors in predicting the development of IR, unlike generally used clinical test values such as LDH.

It is known that sIL-2R is expressed on the surface of activated T cells and is released into the blood as a soluble molecule upon activation; moreover, high sIL-2R levels are detected in lymphoid tumors such as non-Hodgkin's lymphoma (Rubin and Nelson 1990; Setoyama et al. 1994), and tumor mass is a predictive factor for developing IR (Hagberg and Holmbom 2000). In this study, it was shown that a high sIL-2R level (>2,000 U/L) could be a predictive factor for IR after RTX administration, which is consistent with previous studies showing that tumor mass is also associated with an increased risk of IR. However, sIL-2R levels are far easier to determine than tumor mass, and are likely to be of greater clinical relevance.

We also found that IR after RTX can be predicted by low Hb values, probably because this would reflect the presence of a bone-marrow disorder and anemia, and indeed the latter has previously been identified as an IR risk factor (Hong et al. 2013). Blood cell production may be reduced in bone-marrow disorders, which would be reflected by lower Hb levels. Furthermore, secondary anemia may result from reduced erythropoietin levels, caused by chronic inflammation and renal failure due to malignant tumors, although we could not show an association between BUN and Scr levels, which are markers of kidney function, and the development of IR in this study.

In conclusion, we have found that sIL-2R > 2,000 U/L and Hb > LSL are risk factors for IR following RTX administration in patients with B-cell non-Hodgkin's lymphoma, whilst steroid premedication reduces this risk. Therefore, although anti-histamine and antipyretic analgesics are given prior to RTX administration, we suggest that patients with sIL-2R > 2,000 U/L and/or Hb < LSL should also be premedicated with steroids to further reduce the risk of IR.

## 4. Experimental

### 4.1. Patients

Eighty-nine patients with B-cell non-Hodgkin's lymphoma who received RTX for the first time between February 2010 and March 2013, at Gifu Municipal Hospital were enrolled. Patients whose data were missing were excluded.

### 4.2. Categories investigated

The following data were obtained retrospectively using an electronic chart: sex, age, height, weight, tumor type, treatment regimen, body temperature before and after administration, levels of sIL-2R, LDH, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (T-BIL), blood urea nitrogen (BUN), serum creatinine (Scr), and Hb, white blood cell (WBC) and platelet (PLT) counts, and steroid administration immediately before treatment.

IR most often occurs between 30 and 120 min after RTX administration and has symptoms similar to those observed in hypersensitive and allergic reactions including fever, chill, nausea, headache, rash, and fatigue (Dillman 1999; Maloney et al. 1997; Winkler et al. 1999). In this study, the development of IR was considered to be present when the body temperature was above 38 °C (grade 1 fever), which is the standard temperature for onset of fever according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

### 4.3. Statistical analysis

Statistical analysis was performed using IBM SPSS18.0J (IBM, Armonk, NY, USA). A binary variable was applied regarding age groups by categorizing patients into an over 65 year-old group and an under 65 year-old group. Binary variables were applied regarding clinical test values by using the USL for AST, ALT, ALP, T-BIL, BUN, and Scr values, and the LSL for Hb levels, and WBC and PLT counts. Binary variables for LDH and sIL-2R were set at 2 × USL and at 2,000 U/L, respectively, on the basis of previous findings (Yasuda et al. 2014). Patients were divided into two groups, depending on whether they developed IR, and differences between these two groups were tested for significance using a $\chi^2$ test. Furthermore, multiple logistic regression analysis was performed by setting the presence or absence of IR as an objective variable while factors showing $P < 0.25$ by univariate analysis were set as the independent variables. Differences with $P < 0.05$ were considered to be significant.

### 4.4. Ethical considerations

This study was conducted in compliance with the ethical guidelines regarding clinical research after obtaining approval from the ethical committees at Gifu Municipal Hospital and Gifu Pharmaceutical University.

Conflict of interest: There are no conflicts of interest to declare.

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