Yttrium-90 ibritumomab tiuxetan consolidation versus rituximab maintenance therapy after induction chemotherapy in patients with indolent non-Hodgkin lymphoma: a single-institution experience

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ABSTRACT
Objectives: Indolent B-cell non-Hodgkin lymphomas (iNHLs) are considered incurable. Rituximab maintenance and yttrium-90 ibritumomab tiuxetan (90Y-IT) consolidation are promising post-remission therapies. However, only one randomized phase II trial has compared their efficacies and adverse effects. Here, we compared the efficacy and safety of 90Y-IT consolidation and rituximab maintenance in iNHL patients.

Methods: We retrospectively examined 75 iNHL patients with complete or partial response after initial chemotherapy between January 2008 and December 2018. Twenty-seven patients received 90Y-IT consolidation and 48 received rituximab maintenance (every 2 months for 2 years). Progression-free survival (PFS), overall survival (OS), and time to next treatment (TTNT) were estimated from the start of the treatment, and adverse effects were evaluated.

Results: After a median 3.6-year follow-up, the 5-year PFSs of the 90Y-IT consolidation and rituximab maintenance groups were 75.5% and 82.4%, respectively (log-rank test, \( p = 0.839 \)), and the 5-year OSs were 100% and 97.8%, respectively (log-rank test, \( p = 0.465 \)). The corresponding median TTNTs were not reached (log-rank test, \( p = 0.804 \)). The commonest adverse effect with 90Y-IT consolidation was hematotoxicity; lower rates and grades of cytopenia were observed in patients who received rituximab maintenance. Secondary malignancies were observed in 1 patient (4%) who received 90Y-IT consolidation and 2 patients (4.2%) who received rituximab maintenance (Fisher’s exact test, \( p > 0.99 \)).

Conclusion: 90Y-IT consolidation and rituximab maintenance were similar with respect to PFS, OS, and TTNT. However, the features and grades of adverse effects significantly differed. Patient-specific characteristics should be considered when deciding post-remission treatments.

KEYWORDS
Post-remission therapy; radioimmunotherapy; yttrium-90 ibritumomab tiuxetan; rituximab maintenance therapy; indolent non-Hodgkin lymphoma; consolidation therapy; conversion rate; adverse event

Introduction
Indolent B-cell non-Hodgkin lymphoma (iNHL) is one of the commonest lymphoma types, and it generally progresses slowly. Patients with iNHL usually respond to initial treatment but relapse after several years, and the disease seems to be incurable. The main cause of death is lymphoma progression [1]. Therefore, post-remission treatment is an attractive approach to prolong progression-free survival (PFS) and even overall survival (OS).

There are two approaches for post-remission treatment in iNHL, namely, maintenance therapy and consolidation therapy. Rituximab maintenance therapy is a well-established post-remission treatment for patients who responded to first-line chemotherapy. Two-year rituximab maintenance therapy improved PFS in randomized trials [2,3] and OS in a meta-analysis of randomized trials [4]. Therefore, rituximab maintenance therapy has been suggested as a standard of care for patients with iNHL. In contrast, consolidation is a short-term intensive treatment. The efficacy of consolidative radioimmunotherapy (RIT) using yttrium-90 ibritumomab tiuxetan (90Y-IT) was demonstrated in the First-Line Indolent Trial [5]. 90Y-IT comprises ibritumomab covalently linked to tiuxetan, which chelates yttrium-90. Ibritumomab is a murine monoclonal IgG1 antibody against CD20 and the parent of the genetically modified chimeric antibody rituximab. Following the results of early clinical trials [6–8], 90Y-IT was approved for treating recurrent or refractory iNHL in Japan. However, there has been only one retrospective study [9] and one preliminary result from a randomized phase II study comparing rituximab maintenance and RIT in patients with follicular lymphoma (FL) [10]. Therefore, we address the efficacy and safety of 90Y-IT consolidation compared with those of rituximab maintenance in patients with iNHL.

Patients and methods
Patients
This was a retrospective observational study of data from a single institutional database of Yamanashi...
Prefectural Central Hospital. We reviewed the medical records of patients diagnosed with iNHL between January 2008 and December 2018 who received either $^{90}$Y-IT consolidation or rituximab maintenance after achieving partial or better response to one regimen of induction treatment. iNHL included the following CD20-positive subtypes: follicular (grades 1, 2, and 3a), lymphoplasmacytic, small lymphocytic, and marginal zone lymphoma [11]. The study was approved by the ethics committee of Yamanashi Prefectural Central Hospital and was conducted according to the Declaration of Helsinki.

**Treatment procedures**

Patients who completed induction therapy and achieved partial response (PR) or complete response (CR) started either $^{90}$Y-IT consolidation or rituximab maintenance within 2 months. Patients received $^{90}$Y-IT consolidation if they fulfilled the following inclusion criteria: neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and bone lymphoma marrow involvement $<25%$. If the patient desired to receive rituximab maintenance or did not fulfill the criteria, the patient received rituximab maintenance. $^{90}$Y-IT consolidation was performed as follows: the patient received 250 mg/m$^2$ rituximab on days 1 and 8, followed by $^{111}$In ibritumomab tiuxetan (130 MBq $^{111}$In, 1 mg ibritumomab) on day 1 and $^{90}$Y-IT (14.8 MBq/kg, 1 mg ibritumomab) on day 8. The dose of $^{90}$Y was reduced to 11.1 MBq/kg if the patient’s platelet count was $<150 \times 10^9$ on day 8.

Patients in the rituximab maintenance group received 375 mg/m$^2$ rituximab intravenously once every 8 weeks for 2 years or until disease progression, whichever occurred first [3].

**Response to treatment and adverse effects**

The tumor response was assessed according to the Lugano classification [12]. The response to $^{90}$Y-IT consolidation was evaluated 8–12 weeks after therapy, and the response to rituximab maintenance was evaluated at the end of therapy. Adverse effects during $^{90}$Y-IT consolidation or rituximab maintenance were evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.0 [13].

**Statistical analysis**

Patient characteristics and responses to each treatment were analyzed by Fisher’s exact test. PFS, OS, and time to next treatment (TTNT) from the first day of either $^{90}$Y-IT consolidation or rituximab maintenance therapy were assessed according to the revised International Working Group criteria [14], calculated using Kaplan-Meier methods, and then analyzed using a log-rank test with a two-sided significance level of $p = 0.05$ [15]. All statistical analyses were performed using EZR computer software [16].

**Results**

**Patient characteristics**

During the follow-up period, 84 patients with iNHL received induction chemotherapy. Seven patients did not achieve PR or CR, and two patients refused maintenance or consolidation treatment. Therefore, 75 patients ($^{90}$Y-IT consolidation, $n = 27$; rituximab maintenance, $n = 48$) with newly diagnosed iNHL were examined. Of the 48 patients who received rituximab maintenance therapy, 30 patients requested this treatment and 18 patients failed to meet $^{90}$Y-IT consolidation criteria. Baseline characteristics (Table 1) and first-line treatments were well balanced between the two groups. There were no patients with bulky masses (>5 cm) at the baseline of this study. In the

| Parameters | $^{90}$Y-IT consolidation $n = 27$ | R maintenance $n = 48$ | $p$ value$^a$ |
|------------|---------------------------------|-----------------|--------------|
| Patient age, years, median (range) | 67 (45–86) | 65.5 (43–89) | 0.711 |
| Sex, male/female | 15 / 12 | 28 / 20 | 0.335 |
| Performance status, n (%) | 0.99 |
| Stage at diagnosis, n (%) | 0.775 |
| Histopathology, n (%) | 0.341 |
| Bone marrow involvement, n (%) | 0.465 |
| Response to induction therapy, n (%) | 0.158 |
| LDH level, n (%) | > Normal upper limit 2 (7) 25 (93) 0.309 |
| sIL2R level, n (%) | Normal upper limit 2 (7) 3 (11) 0.099 |

**Table 1. Patient characteristics at study entry.**

Abbreviations: $^{90}$Y-IT, yttrium 90-ibritumomab tiuxetan; R, rituximab; MCL, mantle cell lymphoma; CR, complete response; PR, partial response; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; LDH, lactate dehydrogenase; sIL2R, soluble interleukin-2 receptor; NOS, not otherwise specified.

$^a$Fisher’s exact test.
90Y-IT consolidation group, 5 patients received a reduced dose of 90Y (11.1 mBq/kg) owing to platelet counts <150 × 10^9/L.

Efficacy

After a median 3.6-year (range, 0.5–13.1 years) follow-up period, the 5-year PFSSs were 75.5% (95% confidence interval [CI], 48.9–89.5%) and 82.4% (95% CI, 65.1–91.6%) in the 90Y-IT consolidation and rituximab maintenance groups, respectively (log-rank p = 0.839; Table 2, Figure 1A). The median TTNT was not reached in either group (log-rank p = 0.804; Table 2, Figure 1B). The 5-year OSs were 100% (95% CI, 100–100%) and 97.8% (95% CI, 85.3–99.7%) in the 90Y-IT consolidation and rituximab maintenance groups, respectively (log-rank p = 0.465; Table 2, Figure 1C).

In the rituximab maintenance group, 34 patients (71%) completed 2-year rituximab maintenance therapy, 3 (6%) were continuing to receive therapy at the time of the analysis, 5 (10%) discontinued therapy because of progressive disease (PD), and 6 (13%) discontinued therapy because of adverse effects (4 patients) or at the patient’s request (2 patients).

The overall response rates (rates of CR + PR) were 96% and 90% in the 90Y-IT consolidation and rituximab maintenance groups, respectively (Table 2). Thirty-six patients had achieved CR at the start of the post-remission treatment (16 and 20 patients in the 90Y-IT consolidation and rituximab maintenance groups, respectively), and 10 (63%) and 8 (40%) patients in the 90Y-IT consolidation and rituximab maintenance groups, respectively, showed PR to CR conversion after 90Y-IT consolidation or rituximab maintenance (Fisher’s exact test, p = 0.315, Figure 2). In contrast, 1 (4%) and 5 (10%) patients in the 90Y-IT consolidation and rituximab maintenance groups, respectively, did not respond to the treatments or relapsed and received second-line treatments (Fisher’s exact test, p = 0.410, Figure 2). No patient developed transformation to aggressive lymphoma during the follow-up period.

Thirteen patients had relapsed after post-remission treatment (5 and 8 patients in the 90Y-IT consolidation

Table 2. Outcomes after 90Y-ibritumomab tiuxetan consolidation and rituximab maintenance.

| Parameters                  | 90Y-IT consolidation | R maintenance | p value |
|-----------------------------|----------------------|---------------|---------|
| n = 27                      | n = 48               |               |         |
| Response                    |                      |               |         |
| ORR (CR+PR) n               | 26                   | 43            | 0.410^a|
| ORR (CR+PR), %, (95% CI)    | 96 (81–100)          | 90 (77–97)    |         |
| CR n                        | 21                   | 34            | 0.179^a|
| CR rate, %, (95% CI)        | 78 (58–91)           | 71 (56–83)    |         |
| PR n                        | 5                    | 9             |         |
| PR rate, %, (95% CI)        | 18 (6–38)            | 19 (9–33)     |         |
| SD n                        | 1                    | 0             |         |
| SD rate, %, (95% CI)        | 4 (0–19)             | 0 (0–6)       |         |
| PD n                        | 0                    | 5             |         |
| PD rate, %, (95% CI)        | 0 (0–11)             | 10 (4–23)     |         |
| Progression-free survival, 5 years, % | 75.5                  | 82.4         | 0.839^b|
| , 95% CI                   | 48.9–89.5            | 65.1–91.6     |         |
| TTNT %, 95% CI              | NR                   | NR            | 0.804^a|
| Efficacy                    |                      |               |         |
| Overall survival (5 years, %) | 100                  | 97.8         | 0.465^b|
| , 95% CI                   | 100–100              | 85.3–99.7     |         |

Abbreviations: 90Y-IT, yttrium 90-ibritumomab tiuxetan; R, rituximab; ORR, overall response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTNT, time to next treatment; NR, not reached.

^aFisher’s exact test, ^bLog-rank test.

Figure 1. Progression-free survival (A), time to next treatment (B), and overall survival (C) after post-remission treatment. Abbreviations: Yttrium-90 ibritumomab tiuxetan consolidation, red line; rituximab maintenance, dark blue line. 90Y-IT, yttrium-90 ibritumomab tiuxetan.
and rituximab maintenance groups, respectively) at the
time of the analysis. Among them, 11 patients (3 and 8
patients in the \(^{90}\text{Y}-\text{IT consolidation and rituximab main-
tenance groups, respectively}) received rituximab +
bendamustine chemotherapy, and 7 patients (4 and 3
patients in the \(^{90}\text{Y}-\text{IT consolidation and rituximab main-
tenance groups, respectively}) received rituximab mono-
therapy. In the rituximab maintenance group, 4 patients
received \(^{90}\text{Y}-\text{IT} therapy after lymphoma recurrence. One
patient in the rituximab maintenance group received
autologous peripheral blood stem-cell transplantation.

Subgroup analyses by age, sex, histopathology,
stage, bone marrow involvement, and disease status
at the start of post-remission treatment indicated no
significant difference in the 5-year PFS between the
two groups (Table 3).

### Safety

Adverse effects are described in Table 4. Hematologic
toxic effects were the commonest adverse effects in
the \(^{90}\text{Y}-\text{IT consolidation group. Grade 3–4 neutropenia
and grade 3–4 thrombocytopenia 1–2 months after
}\(^{90}\text{Y}-\text{IT consolidation were observed in 22 patients
(81%) and 13 patients (48%), respectively. Eight
patients (30%) received granulocyte colony-stimulating
factor and 8 (30%) received platelet transfusion in the
}\(^{90}\text{Y}-\text{IT consolidation group. One patient (4%) in the
}\(^{90}\text{Y}-\text{IT consolidation group experienced febrile neutro-
penia. Lower rates and lower grades of cytopenia
were observed in the rituximab maintenance group.
The frequencies of non-hematologic adverse effects
were comparable between the two groups. One
patient experienced worsened asthma (to grade 3)
during rituximab maintenance, and treatment was dis-
continued at 18 months. Another patient developed
severe aplastic anemia during rituximab maintenance,
and treatment was discontinued at 10 months.

Secondary malignancies were observed in 2 (4.2%)
and 1 (4%) patient in the rituximab maintenance and
\(^{90}\text{Y}-\text{IT consolidation groups, respectively. In the rituxi-
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### Table 3. 5-year PFS with \(^{90}\text{Y-ibritumomab tiuxetan consolidation versus rituximab maintenance according to subgroup.}

| Factors                      | \(^{90}\text{Y-IT consolidation} | R maintenance | \(^{90}\text{Y-IT consolidation} | R maintenance | p value* |
|------------------------------|-------------------------------|---------------|-------------------------------|---------------|----------|
| Age:                         |                               |               |                               |               |          |
| < 65 years                   | 12                            | 22            | 88.9 (43.3–98.4)             | 79.7 (53.7–92.1) | 0.331    |
| ≥ 65 years                   | 15                            | 26            | 72.2 (53.9–85.4)             | 77.6 (66.2–95.8) | 0.580    |
| Sex:                         |                               |               |                               |               |          |
| Female                       | 12                            | 20            | 90.0 (47.3–98.5)             | 81.7 (55.7–93.3) | 0.631    |
| Male                         | 15                            | 28            | 74.6 (38.4–85.9)             | 83.7 (57.4–94.5) | 0.656    |
| Histopathology:              |                               |               |                               |               |          |
| Follicular lymphoma          | 17                            | 29            | 86.5 (55.8–96.5)             | 75.3 (51.3–88.7) | 0.322    |
| Others                       | 10                            | 19            | 80.0 (66.4–86.5)             | 94.1 (65.0–99.1) | 0.606    |
| Stage:                       |                               |               |                               |               |          |
| I/II                         | 7                             | 9             | 88.6 (21.3–91.2)             | 100            | 0.656    |
| III/IV                       | 20                            | 38            | 76.7 (41.2–92.4)             | 77.5 (57.5–89.3) | 0.583    |
| Bone marrow involvement:     |                               |               |                               |               |          |
| Positive                     | 14                            | 30            | 91.7 (53.9–98.8)             | 79.3 (55.4–91.3) | 0.326    |
| Negative                     | 13                            | 18            | 82.2 (46.3–84.4)             | 88.9 (62.4–97.1) | 0.535    |
| Disease status at the start  |                               |               |                               |               |          |
| of post-remission treatment: |                               |               |                               |               |          |
| CR                           | 16                            | 20            | 84.7 (59.7–94.8)             | 57.7 (37.0–84.3) | 0.115    |
| SD                           | 11                            | 28            | 90.0 (47.3–98.5)             | 82.1 (57.7–93.1) | 0.471    |

Abbreviations: PFS, progression-free survival; \(^{90}\text{Y-IT}, \text{yttrium }90\text{-ibritumomab tiuxetan}; R, rituximab; CI, confidence interval; PR, partial response; CR, complete response.

*Log-rank test.
woman with marginal zone lymphoma) developed breast cancer 18 months after beginning rituximab maintenance. Another patient (a 58-year-old man with FL) developed renal cell carcinoma 110 months after starting rituximab maintenance. In the 90Y-IT consolidation group, 1 patient (an 82-year-old man with FL) developed gastric cancer and prostate cancer 18 and 20 months, respectively, after 90Y-IT consolidation. The frequency of secondary malignancy did not differ between the groups (Fischer’s exact test, \( p > 0.99 \)).

One death (accidental injury) was observed in the rituximab maintenance group at the time of analysis. No patients who were hepatitis B virus carriers (8 and 14 patients in the 90Y-IT consolidation and R maintenance groups, respectively) had developed hepatitis B virus reactivation at the time of analysis.

**Discussion**

90Y-IT consolidation and rituximab maintenance after induction chemotherapy improve PFS, with hazard ratios of 0.40–0.55 and 0.465, respectively [2,3,17]. However, only one prospective randomized trial directly compared outcomes after 90Y-IT consolidation and rituximab maintenance treatments [10].

In this study, we evaluated the efficacy of 90Y-IT consolidation compared with that of rituximab maintenance after induction therapy in patients with iNHL in terms of PFS, OS, and TTNT. Of the 48 patients who received rituximab maintenance therapy, 30 patients preferred this treatment to 90Y-IT consolidation because of their prior experience with rituximab administration. The 5-year PFS were 75.5% and 82.4% in the 90Y-IT consolidation and rituximab maintenance groups, respectively. 90Y-IT consolidation and rituximab maintenance also showed similar OS and TTNT rates. The CR rates were 78% and 71% in the 90Y-IT consolidation and rituximab maintenance groups, respectively. The conversion rates from PR to CR in the 90Y-IT consolidation and rituximab maintenance groups were 63% and 40%, respectively. These conversion rates are compatible with those reported previously [17]. The conversion rate in the 90Y-IT consolidation group tended to be higher than that in the rituximab maintenance group, but the difference was not significant. In the rituximab maintenance group, 5 patients experienced PD, but PD was not observed in the 90Y-IT consolidation group. These data indicate 90Y-IT consolidation might have benefit for short-term disease control. In subgroup analysis, we observed no significant differences between patients in the two groups when examining any of the categories. These results suggest that 90Y-IT consolidation and rituximab maintenance have similar efficacy in all analyzed categories of patients.

However, these two post-remission treatments had different outcomes in terms of adverse effects. Hematologic toxicity in the short term and secondary malignancy in the long term are major concerns in patients treated with RIT [5]. Among patients receiving 90Y-IT consolidation therapy in this study, 22 (81%) experienced grade 3–4 neutropenia, 13 (48%) experienced grade 3–4 thrombocytopenia, 8 (30%) received granulocyte colony-stimulating factor, 8 (30%) received platelet transfusion, and 1 (4%) developed febrile neutropenia and needed to receive antibiotics. However, no life-threatening hematologic or non-hematologic adverse effects were observed. Moreover, no patients developed acute myeloid leukemia or myelodysplastic syndrome, and no difference was observed in the frequency of secondary solid tumors between the two groups. A previous study indicated that the CD34-positive cell yield was significantly lower in patients previously treated with 90Y-IT consolidation than in patients who did not undergo RIT [18]. We also experienced difficulty in

### Table 4. Adverse events of 90Y-ibritumomab tiuxetan consolidation and rituximab maintenance.

| Adverse event | 90Y-IT consolidation (n = 27) | R maintenance (n = 48) |
|---------------|-----------------------------|----------------------|
| Any event     | 27 (100) 20 (74)            | 9 (19) 2 (4)         |
| Hematologic   |                             |                      |
| Neutropenia   | 25 (94) 22 (81)             | 7 (15) 2 (4)         |
| Anemia        | 18 (67) 0                   | 2 (4) 1 (2)          |
| Thrombocytopenia | 27 (100) 13 (48)   | 4 (8) 1 (2)          |
| Non-hematologic |                           |                      |
| Fatigue       | 8 (30) 0                   | 4 (8) 0              |
| Infusion-related reaction | 0 0 | 0 0 |
| Asthma        | 0 0                        | 1 (2) 0              |
| Hypoproteinemia | 7 (26) 0                | 8 (17) 0             |
| Hypoalbuminemia | 2 (7) 0                   | 3 (6) 0              |
| Increased bilirubin | 0 0           | 1 (2) 0              |
| Increased ALT | 5 (19) 0                   | 6 (13) 0             |
| Increased ALP | 5 (19) 0                   | 11 (23) 0            |
| Increased Cr  | 7 (26) 0                   | 5 (10) 0             |
| Hypoalbuminemia | 0 0                        | 3 (6) 0              |
| Increased ALP | 0 0                        | 4 (8) 0              |
| Thrombocytopenia | 27 (100) 13 (48)   | 4 (8) 1 (2)          |
| Neutropenia   | 25 (94) 22 (81)             | 7 (15) 2 (4)         |
| Anemia        | 18 (67) 0                   | 2 (4) 1 (2)          |
| Thrombocytopenia | 27 (100) 13 (48)   | 4 (8) 1 (2)          |
| Non-hematologic |                           |                      |
| Fatigue       | 8 (30) 0                   | 4 (8) 0              |
| Infusion-related reaction | 0 0 | 0 0 |
| Asthma        | 0 0                        | 1 (2) 0              |
| Hypoproteinemia | 7 (26) 0                | 8 (17) 0             |
| Hypoalbuminemia | 2 (7) 0                   | 3 (6) 0              |
| Increased bilirubin | 0 0           | 1 (2) 0              |
| Increased ALT | 5 (19) 0                   | 6 (13) 0             |
| Increased ALP | 5 (19) 0                   | 11 (23) 0            |
| Increased Cr  | 7 (26) 0                   | 5 (10) 0             |
| Hypoalbuminemia | 0 0                        | 3 (6) 0              |
| Increased ALP | 0 0                        | 4 (8) 0              |
| Thrombocytopenia | 27 (100) 13 (48)   | 4 (8) 1 (2)          |
| Neutropenia   | 25 (94) 22 (81)             | 7 (15) 2 (4)         |
| Anemia        | 18 (67) 0                   | 2 (4) 1 (2)          |
| Thrombocytopenia | 27 (100) 13 (48)   | 4 (8) 1 (2)          |

Abbreviations: 90Y-IT, yttrium 90-ibritumomab tiuxetan; R, rituximab; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; Cr, creatinine.
collecting hematopoietic stem cells from peripheral blood. This patient was administered 90Y-IT as consolidation after the first relapse (the case is not included in this study for this reason). Because autologous hematopoietic stem cell transplantation after 90Y-IT consolidation is considered in many patients, we should be aware of this issue. Regarding rituximab maintenance, previous studies [3,19,20] found that infection is the commonest adverse effect. However, this therapy seems to be well tolerated, with a limited number of adverse effects resulting in treatment discontinuation, and easy to administer, and no increased risk of secondary malignancy or effect on hematopoietic stem cell collection. In this study, mild hypoproteinemia, which manifests as a decrease in serum immunoglobulin levels, was observed in eight patients, and the incidence of infectious events was not increased in the rituximab maintenance group. In previous studies [3,21], withdrawal from rituximab maintenance because of toxicity was observed in approximately 4% of patients. In this study, 2 of 48 patients (4.2%) withdrew treatment. One of these patients experienced worsening asthma, and another developed aplastic anemia during rituximab maintenance, necessitating discontinuation of rituximab maintenance therapy. Previous studies reported recurrent infections, neutropenia, severe allergic reaction, or arrhythmias as reasons for withdrawal from rituximab maintenance [21,22]. Worsening asthma and aplastic anemia were not observed in previous studies. The patient who developed aplastic anemia had concomitant autoimmune disease, which may have contributed to developing aplastic anemia. Further studies with a greater number of patients are necessary to obtain information about these adverse effects.

There are some practical considerations needed to decide between RIT and rituximab maintenance therapy. First, a previous phase III study that compared rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) vs. CHOP followed by RIT induction treatment in patients with FL [23], negative TP53 mutations [24], and normal serum β2-microglobulin (sβ2MG) at diagnosis [25] showed longer PFS in CHOP-RIT patients. Therefore, RIT might be suitable for low risk patients. Second, 90Y-IT treatment is not readily available at all institutions [26], and primary physicians need to refer patients to an institution where 90Y-IT treatment is available. Patient accessibility is also an important factor to consider. Additionally, in Japan, the cost of 90Y-IT treatment is approximately 50,000 US dollars. The cost of rituximab maintenance for 2 years (12 treatment cycles) is approximately 20,000 US dollars. Moreover, if the patient instead receives biosimilar rituximab, the cost of rituximab maintenance is 30% lower. Therefore, rituximab maintenance seems more economically preferable.

Recently, post-remission 131I-tositumomab RIT followed by 4-year rituximab maintenance in untreated FL patients was investigated in a single-arm trial [27]. This trial showed excellent outcomes, with 3- and 5-year PFS of 90% and 85%, respectively. However, only 41 (59%) of 69 patients proceeded to maintenance treatment and completed 4-year rituximab maintenance. The authors concluded that 4-year rituximab maintenance is not feasible for many patients. Because PFS in that study was similar to the 5-year PFS we observed with both 90Y-IT consolidation and rituximab maintenance post-remission treatments, post-remission treatments using RIT consolidation followed by rituximab maintenance may be overtreatment for iNHL.

Obinutuzumab-based immunochemotherapy followed by obinutuzumab maintenance achieves longer PFS than rituximab maintenance in patients with FL [28]. In the obinutuzumab era, we might need further investigation to compare 90Y-IT consolidation and rituximab maintenance with obinutuzumab maintenance in real-world settings.

This study has several limitations. Our study was non-randomized, retrospective, and based on a small number of patients with heterogeneous histopathological iNHL. Because of the indolent nature of iNHL, long-term follow-up is needed to confirm prognosis and adverse effects, including the potential for secondary malignancies in patients who received 90Y-IT consolidation treatment. Large-scale randomized studies are necessary to confirm our results.

A clinical decision about which treatment, 90Y-IT consolidation or rituximab maintenance, is preferable as a post-remission therapy should be based on the effectiveness, adverse effects, convenience, and cost of treatment, as well as biological features of the lymphoma. For example, if it is too difficult for the patient to visit the hospital every 2 months for 2 years, 90Y-IT consolidation is preferable because there are few adverse effects after the period of post-treatment myelosuppression. Patients who achieved only PR after induction treatment, had FL with normal sβ2MG, or had no TP53 mutation at diagnosis might also benefit from 90Y-IT consolidation. In contrast, we should adopt rituximab maintenance therapy for women of childbearing age.

In conclusion, we indicated that 90Y-IT consolidation has similar efficacy to rituximab maintenance as a post-remission treatment in terms of PFS, OS, and TTNT in real-world settings. However, these treatments have different characteristics and adverse effect profiles. Patient backgrounds should be assessed to determine which treatment would be more suitable.

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