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ORIGINAL ARTICLE

Repeated radioimmunotherapy with ^{131}I-rituximab for patients with low-grade and aggressive relapsed or refractory B cell non-Hodgkin lymphoma

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Abstract
Purpose A single treatment of ^{131}I-rituximab in patients with B cell non-Hodgkin lymphoma (NHL) showed a modest rate of response (29 %) in a relatively short duration (median 2.9 months). On the basis of this result, we investigated whether repeated treatment with ^{131}I-rituximab could improve the response.
Patients and methods Thirty-one patients with relapsed or refractory B cell NHL received unlabeled rituximab (70 mg) immediately prior to the administration of a therapeutic dose of ^{131}I-rituximab. The tumor response was evaluated 1 month later by contrast-enhanced ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. Radioimmunotherapy (RIT) was repeated at 4-week intervals.
Results A total of 87 cycles of RIT were administered. Repeated RIT yielded twofold increases in response rate (68 %) and in median response duration (8.6 months). This protocol also induced a favorable response in patients with an aggressive histology compared to that induced by a single treatment (50 vs. 9 %, respectively, $p = 0.063$). The toxicities were principally hematologic with grade 4 thrombocytopenia occurring in 12 % and neutropenia occurring in 17 % of the 85 assessable cycles.
Conclusions Compared to a single treatment, repeated RIT with ^{131}I-rituximab increased the response rate and duration for patients with relapsed or refractory B cell NHL, including those with an aggressive histology.

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Introduction

Radioimmunotherapy (RIT) uses therapeutic radioisotopes that are chemically conjugated to monoclonal antibodies (mAb) or mAb-derived constructs targeted to the tumor. This type of treatment is aimed at improving the clinical response rates attained with unconjugated antibodies. For example, anti-CD20 antibodies radiolabeled with yttrium-90 (^{90}Y)-ibritumomab tiuxetan (Zevalin, Biogen Idec Inc, San Diego, CA, and Schering AG, Berlin, Germany) or iodine-131 (^{131}I)-tositumomab (Bexxar, Corixa Corp, Seattle, WA) are commercially available for relapsed non-Hodgkin lymphoma (NHL).These treatments have achieved overall response rates (ORR) of 75 to 80 % with a response duration of 10–14 months, including a complete response (CR) in 20–50 % of the patients [1, 2]. Similarly, Turner et al. performed RIT using radioiodinated human/murine chimeric anti-CD20 mAb rituximab (^{131}I-rituximab) and reported an ORR of 76 % and a high CR or unconfirmed CR (53 %) after a single treatment of ^{131}I-rituximab in 91 patients with relapsed or refractory indolent NHL [3]. In addition, they were able to decrease the cost of RIT by using ^{131}I-rituximab as compared to other commercial RIT drugs (^{90}Y-ibritumomab and ^{131}I-tositumomab).

On the basis of these observations, we evaluated the efficacy, safety, and toxicity of ^{131}I-rituximab RIT for treating a Korean population with B cell NHL. Approval for this study was obtained from the Korean Food Drug Administration (KFDA). Between May 2004 and October 2006, 24 patients received a single treatment with ^{131}I-rituximab, and they showed a modest response rate (29 %) with a relatively short response duration (median 2.9 months) [4]. Even though these findings are limited to low-grade (LG) B cell NHL (ORR 46 %, and median progression-free survival (PFS) 4.5 months), they are relatively inferior to those of ^{131}I-rituximab reported by Turner et al. [3]. The less favorable results of our previous study may be due to the relatively lower dose of unlabeled mAb that was used compared to the doses of unlabeled cold rituximab that were used in the study by Turner et al. In our previous study, a dose of 70 mg of unlabeled rituximab was given immediately prior to the administration of a therapeutic dose of ^{131}I-rituximab, whereas 65 % (59/91) of the patients in Turner et al.'s study received four doses of 375 mg/m^2 rituximab before and after RIT with ^{131}I-rituximab. By excluding the possible contribution of large amounts of unlabeled rituximab, we have demonstrated the activity of ^{131}I-rituximab alone.

These results suggest that a single RIT could be improved by repeated RIT according to the same logical principal that chemotherapy for cancer induces a log-linear reduction in tumor volume by repeating the same chemotherapy drug. Here, we investigated whether repeated administration of ^{131}I-rituximab at regular intervals could increase the RIT response compared to a single administration of radiolabeled mAb.

Patients and methods

Study design and objectives

The repeated RIT protocol used in this study was a phase II, single-arm, open-label study of the safety and efficacy of subsequent repeated administration of ^{131}I-rituximab in patients with relapsed or refractory B cell NHL who had no progress after a single treatment with the same drug. The primary endpoint of the study was to evaluate the response rate of repeated treatment with ^{131}I-rituximab as compared to that of a single treatment with the same drug. The secondary endpoints were to evaluate the toxicities, time to progression, and overall survival (OS). Co-investigators from five institutes in Korea participated in this study and referred their eligible patients to our hospital. The protocol was approved by the KFDA and the institutional review board of the Korea Cancer Center Hospital.

Patients

Patients who had histologically confirmed CD20-positive relapsed or refractory B cell NHL and at least one measurable lesion with the longest diameter being ≥1 cm on contrast-enhanced ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) were considered eligible for this study. In addition, the patients had to be 19–75 years old with an Eastern Cooperative Oncology Group performance status of 0–2, adequate liver function (total serum bilirubin level <1.5 times the upper normal limit (UNL) and serum transaminases levels <2 times the UNL [<5 times the UNL for patients with liver involvement]), adequate renal function (serum creatinine level <1.5 mg/dL), and adequate bone marrow (BM) function (absolute neutrophil count [ANC] ≥1.5 × 10^9/L, hemoglobin level ≥10.0 g/dL, and platelet count ≥100 × 10^9/L). No more than 25 % of the hematopoietic marrow space could be involved with lymphoma on BM biopsy. Patients who had previously received rituximab were eligible. The exclusion criteria included significant impairment of cardiac, renal, or hepatic function or the administration of chemotherapy or radiotherapy within 4 weeks of the start of the study. All patients provided their written informed consent before enrollment.

Treatment

All the patients were treated as inpatients. Before infusing the unlabeled rituximab, patients were premedicated with acetaminophen, diphenhydramine, and a serotonin antagonist. In addition, to prevent thyroid uptake of ^{131}I, potassium iodine was administered at least 24 h before RIT and continued for 14 days. Iodination of the antibody was accomplished using Iodo-Beads (Pierce Chemical Co, Rockford, IL, USA) in our radiochemical laboratory, according to the previously described method [4]. The labeling yield was determined by performing radio-thin-layer chromatography using silica-coated glass and acetone as a developing solution.

The RIT schedule consisted of an infusion of 70 mg of unlabeled rituximab to optimize the biodistribution and tumor targeting of ^{131}I-rituximab followed by a therapeutic dose of radioiodide labeled with 30 mg of rituximab diluted in 150 ml of normal saline that was infused over 1 h. A dose of 200 mCi of radioiodide was used in the first administration of ^{131}I-rituximab for each patient. The dose of radioiodide in the subsequent administration of ^{131}I-rituximab was either 200, 150, or 100 mCi according to the grade of hematological toxicities that occurred after the previous treatment of ^{131}I-rituximab.

The response to treatment was assessed based on physical examinations, laboratory data, and ^{18}F-FDG PET/CT with enhancement via contrast dye at 1 month after RIT. If a patient did not progress, then subsequent readministration of ^{131}I-rituximab was performed at 4-week intervals when the laboratory values fit the inclusion criteria. RIT was continued until disease progression or up to a maximum of six cycles. After the last treatment with ^{131}I-rituximab, response evaluation was performed every 3 months during the first 2 years and then every 6 months until disease progression.

Estimation of the dose absorbed by the bone marrow

Prior to acquiring the emission images, blank and transmission scans were performed using a cobalt 57 (Co-57) sheet source for correcting the attenuation. After administration of ^{131}I-rituximab, anterior and posterior whole-body scans and blood samples were obtained at 5 min and at 6, 24, 48, 72, and 240 h. Scans were obtained using a gamma camera (Scintron, MiE, Germany) with a high-energy collimator. Radioactivity in the blood samples was measured after 3-week decay with a gamma counter (1470 WIZARD; PerkinElmer, Waltham, MA, USA). The whole-body planar images were acquired using six standard source vials that contained various amounts of radioactivity in 10 mL of saline placed beside the patient in the field of view. All the emission images were converted to geometric mean images with corrections for the dead time. The time–activity curves for the whole body and blood were generated, and these were used to estimate the residence time and dose absorbed by the whole body and BM by using the MIRDOSE 3 program (The Society of Nuclear Medicine, Reston, Virginia, USA) [5].

Response and toxicity evaluation

The response evaluation was in accordance with the International Workshop of Standardized Response Criteria for NHL [6]. Toxicity was evaluated before each ^{131}I-rituximab treatment according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0. If the patient had hematological toxicities higher than grade 3, hematological assessment with full blood counts was carried out weekly from the occurrence of those toxicities until they dipped below grade 2 or returned to baseline values. Thyroid function was monitored at 3-month intervals.

Statistical methods

The chi-square test was used to compare the response rates between subgroups according to the type of histology and the type of RIT protocol. The binary logistic regression test was used to analyze the risk factors related to hematological toxicities following RIT with ^{131}I-rituximab. The Kaplan–Meier method was used to estimate the PFS and the OS.

Results

Patients

Between July 2005 and February 2012, 31 patients were enrolled in the repeated RIT with ^{131}I-rituximab protocol. The baseline characteristics of the patients are shown in Table 1. Of 31 patients, 24 (77 %) had no history of prior RIT with ^{131}I-rituximab, while seven (23 %) had shown a favorable response or stabilization (1 CR, 3 partial responses [PRs], and 3 stable diseases [SDs]) after a single treatment with ^{131}I-rituximab. All those patients with the exception of one were enrolled in the repeated RIT protocol after they displayed progression with a single treatment of ^{131}I-rituximab. The median time from the initial treatment with ^{131}I-rituximab to repeated RIT for these seven patients was 6.4 months (range 2.5–10.8 months). The patient who was excluded had follicular lymphoma and had previously received three cycles of fludarabine every 4 weeks and weekly rituximab for 4 weeks after a progression with the initial treatment of ^{131}I-rituximab.

Table 1 Patient characteristics ($n = 31$)

Characteristic	No.	%
Age (years)		
Median	63.0	
Range	26–75	
≥60	17	55
Sex		
Male	21	68
Female	10	32
Tumor histology		
Mantle cell lymphoma	12	39
Diffuse large B cell lymphoma	7	23
Marginal zone B cell lymphoma	6	19
Follicular lymphoma	4	13
Burkitt's lymphoma	1	3
Small lymphocytic lymphoma	1	3
IPI at study entry		
0–1	10	32
2	14	45
3	5	16
4–5	2	6
Stage at study entry		
I or II	7	23
III or IV	24	77
LDH at study entry		
Normal	23	74
Elevated	8	26
Maximum tumor diameter		
<5 cm	26	84
≥5 cm	5	16
No. of previous chemotherapies (cycles)		
Median	8	
Range	5–36	
Prior rituximab		
Yes	20	65
No	11	36
Prior radiotherapy		
Yes	4	13
No	27	87
Response to prior chemotherapy		
Relapsed	21	68
Refractory	10	32
Months from NHL diagnosis to study entry (months)		
Median	26.0	
Range	5.5–150.7	

This patient showed a PR to rituximab treatment, but 6 months later, he had tumor progression and was then enrolled in the repeated RIT protocol.

The dose absorbed by the whole body and bone marrow

A total of 87 treatments (median 2; range 1–6) of ^{131}I-rituximab were performed for all 31 patients. The median interval between the prior and the next administration of ^{131}I-rituximab was 56 days (range 28–400 days). The median dose of the administered radioiodide during the 87 treatments was 7.4 GBq (range 3.7–8.5 GBq). The median total dose of ^{131}I administered to each patient over the entire study treatment period was 501 mCi (18.5 GBq; range 198–1,188 mCi [7.3–43.9 GBq]).

Dosimetry data could be collected for all administered doses in 17 patients (45 therapy doses of ^{131}I-rituximab). In 14 patients, some data points were missing due to the patient's refusal or the errors in logistics. For the 17 patients who were assessable for dosimetry, during each therapy dose of ^{131}I-rituximab (median 7.4 GBq; range 5.6–7.5 GBq), the median delivered dose was 26 rad (range 12–95 rad) and 38 rad (range 12–161 rad) to the whole body and BM, respectively. And the median dose of total ^{131}I administered to each patient was 416 mCi (15.4 GBq; range 200–1,188 mCi), and the total delivered median dose was 79 rad (range 12–166 rad) and 156 rad (range 14–305 rad) to the whole body and BM, respectively. In addition, the mean effective whole-body half-life of ^{131}I-rituximab was 47.5 h (range 11.5–161.2 h).

Response

Objective responses were observed in 21 (68 %) patients (95 % CI 52–84; Table 2). These ORR are nearly twofold higher than that of the single RIT protocol of ^{131}I-rituximab (68 vs. 29 %).

A statistically significant difference between the responses in patients with LG and the patients with aggressive B cell NHL (46 vs. 9 %, $p = 0.049$; Supplementary Table 1) was observed in the patient population that underwent the previous single RIT protocol of ^{131}I-rituximab. However, no significant difference was observed in terms of the response of the patients in the repeated RIT protocol of ^{131}I-rituximab between these two subgroups (78 vs. 50 %, $p = 0.381$). In other words, the repeated RIT of ^{131}I-rituximab can induce a favorable response even in patients who have aggressive histology (diffuse large B cell lymphoma and Burkitt's lymphoma) as compared to the single RIT of ^{131}I-rituximab (50 vs. 9 %, $p = 0.063$). In addition, a threefold increase in terms of the duration of the response was observed in patients who underwent the repeated RIT with ^{131}I-rituximab compared to that observed in patients who underwent the single treatment with the same drug (median 8.6 months; range 1.1–69.8 months vs. median 2.9 months; range 1.1–64.9 months).

Table 2 Response

Response	No. of patients ($n = 31$)	Histology					
		MCL ($n = 12$)	DLBCL ($n = 7$)	MZBCL ($n = 6$)	FL ($n = 4$)	Burkitt ($n = 1$)	SLL ($n = 1$)
CR	13 (42 %)	4 (33 %)	1 (14 %)	5 (83 %)	2 (25 %)	1 (100 %)	0
PR	8 (26 %)	3 (25 %)	2 (29 %)	1 (17 %)	2 (75 %)	0	0
SD	7 (22 %)	5 (42 %)	1 (14 %)	0	0	0	1 (100 %)
PD	3 (10 %)	0	3 (43 %)	0	0	0	0
ORR	21 (68 %)	8 (58 %)	3 (43 %)	6 (100 %)	4 (100 %)	1 (100 %)	0
Duration of response (months)							
Median	8.6	5.7	5.0	16.8	2.5	9.4	
Range	1.1–69.8	1.1–26.6	1.1–69.8	8.6–58.5	1.7–29.2		

MCL mantle cell lymphoma, *DLBCL* diffuse large B cell lymphoma, *MZBCL* marginal zone B cell lymphoma, *FL* follicular lymphoma, *Burkitt* Burkitt's lymphoma, *SLL* small lymphocytic lymphoma, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* objective response rate

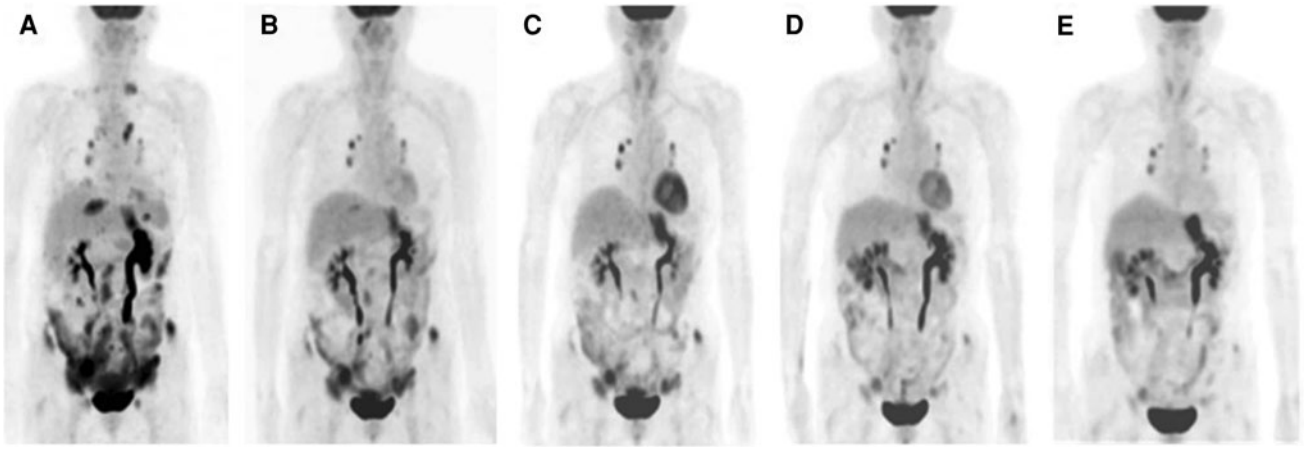

Fig. 1 Serial images of ^{18}F-FDG PET/CT showing a decrease in tumor volume following repeated RIT with ^{131}I-rituximab (*A*) Baseline image from a patient with relapsed marginal zone B cell lymphoma involving multiple lymph nodes (the supraclavicular, mediastinal, intra-abdominal/pelvic, and inguinal nodes) and left-sided hydronephrosis. The images *B* to *E* were taken at 1 month after the first (*B*), second (*C*), third (*D*), and fourth (*E*) administration of ^{131}I-rituximab, respectively. Both hilar lymph nodes were assessed as benign lymphadenopathy because they showed no change during repeated RIT and no calcification on the CT image. After four treatments of ^{131}I-rituximab, the patient achieved a partial response

Figure 1 shows the serial images of ^{18}F-FDG PET/CT of a patient who had relapsed marginal zone B cell lymphoma and had received four treatments of ^{131}I-rituximab. This figure clearly shows that the tumor volume subsequently decreased with repeated administration of ^{131}I-rituximab.

Survival

After a median follow-up of 21.8 months (range 1.6–79.7 months), the median PFS for all the patients was 9.8 months (95 % CI 7.9–11.7 months) (Fig. 2a). The median OS was 48.2 months (95 % CI 41.7–54.7 months) with a 5-year survival rate of 42 % (Fig. 2b). In terms of survival, no significant difference was observed between the two histological subgroups. However, in the patient population that underwent the previous single treatment protocol of ^{131}I-rituximab, statistically significant differences were observed between the LG and aggressive B cell NHL for the median PFS (4.5 vs. 1.3 months, $p = 0.0007$) (Fig. 2c) and median OS (30.3 vs. 6.5 months, $p = 0.0295$; Fig. 2d). The survival results for the two types of RIT protocols using ^{131}I-rituximab also showed that repeated RIT is more effective, even for aggressive histology, compared to the single RIT treatment, in agreement with response findings.

Adverse events

Of the 87 ^{131}I-rituximab treatments for 31 patients, 85 were assessable for toxicities. Two treatments were not

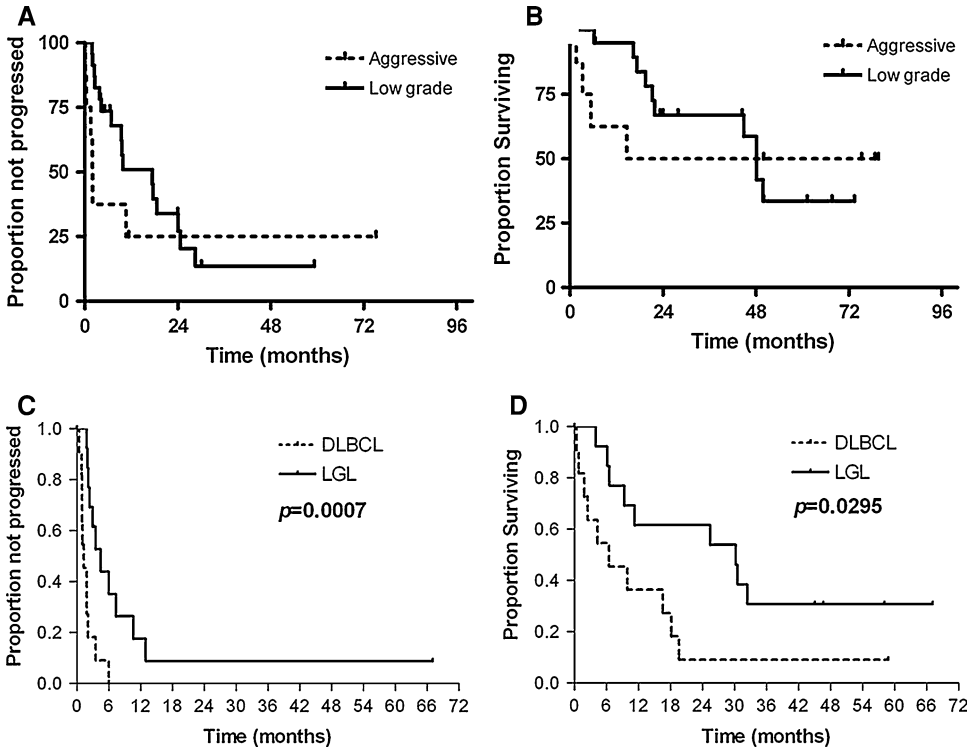

Fig. 2 Progression-free survival (PFS) and overall survival (OS), repeated RIT with ^{131}I-rituximab ($n = 31$) (**a** and **b**). PFS and OS, single treatment with ^{131}I-rituximab ($n = 24$) (**c** and **d**). Reprinted with permission [4]

assessable because the patients were lost to follow-up. The toxicities were principally hematologic with grade 4 thrombocytopenia occurring in 12 % (10/85) and grade 4 neutropenia occurring in 17 % (14/85) of the cases (Table 3). Fifteen (52 %) patients required platelet transfusion, seven (24 %) required packed red blood cells, and 14 (48 %) received granulocyte colony-stimulating factor. Antibiotics were administered to seven patients with grade 4 neutropenia for prophylaxis of infection, but none of the patients had febrile neutropenia. One patient was hospitalized for transfusion and for close observation because of grade 4 hematological toxicities. The median time to the nadir of the hematological toxicities higher than grade 3 was 33 days for platelets and 44 days for neutrophils. Two patients with grade 4 hematological toxicities, despite the lack of BM involvement at the time of study entry, needed

Table 3 Hematological toxicities

	Repeated treatment		Single treatment ($n = 24$)
	Per patient ($n = 29$)	Per treatment ($n = 85$)	
G3 or 4 neutropenia[a]	21 (72 %)	28 (33 %)	5 (21 %)
Median time to nadir, days (range)	44 (11–102)		32 (32–35)
Median duration of toxicity[b], days	16 (1–156)	6 (1–7)	
Requiring G-CSF	14 (48 %)	16 (19 %)	3 (13 %)
G3 or 4 thrombocytopenia[a]	19 (66 %)	22 (26 %)	8 (34 %)
Median time to nadir, days (range)	33 (25–106)		31 (8–41)
Median duration of toxicity[b], days	28 (11–239)		6 (1–56)
Requiring PC transfusion	15 (52 %)	18 (21 %)	6 (25 %)
G3 or 4 anemia[a]	4 (14 %)	4 (5 %)	1 (4 %)
Median time to nadir, days (range)	61 (32–102)		37
Median duration of toxicity[b], days	16 (2–29)		1
Requiring packed RBC transfusion	7 (24 %)	8 (9 %)	2 (8 %)

G-CSF granulocyte colony-stimulating factor, *PC* platelet concentrate, *RBC* red blood cell

[a] According to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0

[b] Interval time from the development of grade 3 or 4 hematological toxicities to recovery above grade 2 or baseline

longer than 6 months for recovery to toxicities below grade 2 (Supplementary Table 2).

One patient (patient 1), a 63-year-old woman, had a history of six cycles of CVP (cyclophosphamide, vincristine, and prednisolone) for her marginal zone B cell lymphoma. She received administration of ^{131}I-rituximab once a month for 3 months and achieved a CR. However, after the third ^{131}I-rituximab treatment, she developed grade 4 thrombocytopenia, grade 4 neutropenia, and grade 3 anemia. Supportive treatments were administered for almost 10 months, and the patient fully recovered to the baseline complete blood counts at 1 year from the last RIT and has sustained a CR for 58 months.

Another patient (patient 2), a 49-year-old man, had a history of one cycle of CVP and five cycles of CHOP (CVP plus doxorubicin). He was initially enrolled in the single treatment with ^{131}I-rituximab protocol and achieved SD status. However, his disease progressed 2 months after RIT. After that, the patient received four cycles of fludarabine every 4 weeks and four weekly rituximab treatments before enrollment into the repeated RIT protocol. He then received administration of ^{131}I-rituximab once a month for 3 months and achieved a PR for 3 months. However, he experienced grade 4 thrombocytopenia, grade 4 neutropenia, and grade 3 anemia, all of which slowly recovered to the grade 2 level 2 years from the last RIT. Two examinations of the BM were performed to exclude BM involvement with the progression of lymphoma during grade 3 or 4 myelosuppression; there was no evidence of BM involvement of lymphoma. Unfortunately, however, the patient was diagnosed with unclassifiable myelodysplastic syndrome (MDS) approximately 3 years from the last RIT and died 1 year later.

In addition, another patient, a 56-year-old woman, developed MDS (refractory anemia with excess blast-2 [RAEB-2]) 52 months after the first treatment with ^{131}I-rituximab. She had a history of six cycles REPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin) and a single treatment with ^{131}I-rituximab. She underwent the repeated RIT protocol after progression following a single RIT and received four administrations of ^{131}I-rituximab every 6 months. This patient achieved PR for 30 months with repeated RIT when she developed RAEB-2 and was referred to another institute for allogeneic hematopoietic stem cell transplantation. The patient died 18 months later.

Risk factors related to the development of grade 4 hematological toxicities were analyzed and are shown in Table 4. A statistical correlation between the total number of previous chemotherapy sessions and the grade of the hematological toxicities was observed in patients who received a single treatment of ^{131}I-rituximab. In contrast, the statistically significant effect of previous chemotherapy on the hematological toxicities of RIT disappeared in the cases with repeated treatment with ^{131}I-rituximab. For grade 4 thrombocytopenia, three or more administrations of ^{131}I-rituximab and normal lactate dehydrogenase value at the time of entry into the study were statistically significant risk factors. Patients with aggressive histology and those over 60 years of age showed increased development of grade 4 thrombocytopenia and grade 4 neutropenia, respectively.

Discussion

Current guidelines from the National Comprehensive Cancer Network recommend RIT as a first-line therapy (category 2B) for patients with follicular lymphoma and the elderly or infirm (category 2A), as a first-line consolidation

Table 4 Univariate analysis of risk factors related to the development of grade 4 neutropenia or thrombocytopenia

Risk factor	G4 neutropenia	G4 thrombocytopenia
No. of prior chemotherapy regimens (<3 vs. ≥3)	0.329	0.706
Histology (LG vs. aggressive)	0.528	0.079
Maximum tumor diameter (<5 cm vs. ≥5 cm)	0.219	0.670
Prior rituximab (no vs. yes)	0.958	0.525
BM involvement at study (no vs. yes)	1.000	1.000
Age (<60 vs. ≥60)	0.053	0.913
LDH (normal vs. >normal)	0.119	0.029
Stage at study (I/II vs. III/IV)	0.456	0.594
Prior radiotherapy (no vs. yes)	0.999	0.999
Dose of radioiodine (<7.4 GBq vs. ≥7.4 GBq)	0.438	0.452
Number of ^{131}I-rituximab (≤2 vs. ≥3)	0.589	0.037
The time of ^{131}I-rituximab residing in BM (<1.0 h vs. ≥1.0 h)	0.758	0.472

Three or more administrations of ^{131}I-rituximab and normal value of LDH at the study entry are statistically associated with the development of the grade 4 thrombocytopenia

LG low-grade lymphoma, *Aggressive* aggressive histology lymphoma, *BM* bone marrow, *LDH* lactate dehydrogenase

agent (category 1), and as a second-line and subsequent therapy agent (category 1) [7]. However, despite increasing evidence of the efficacy and safety of RIT in NHL, this "designer" targeted therapy is not routinely used. Schaefer et al. investigated the pattern of RIT use by nuclear physicians, radiation oncologists, medical oncologists, and hematologists in the United States through a survey involving two e-mails [8, 9] and found that barriers to the use of RIT included difficulty in referral, perceptions of high treatment cost, concerns about negative financial outcomes related to referral, and lack of training for the use of these drugs. These findings suggested that successful integration of RIT into the clinical arena would require more focus not only on scientific evidence but also on logistic and economic issues.

To increase the frequency and durability of responses to RIT in NHL, different strategies have been developed including myeloablative or fractionated RIT. Press et al. [10] demonstrated that a single, large dose of ^{131}I-labeled mouse B1 antibody (anti-CD20) with autologous stem cell transplantation had remarkable efficacy for NHL. Although late relapses do occur, a single myeloablative RIT with ^{131}I- or ^{90}Y-labeled mAb usually leads to long-term durable remissions [11, 12]. These findings indicate that additional treatment is needed to eradicate undetectable disease in NHL patients who have responded to a single RIT even if it was a myeloablative dose. Moreover, myeloablative RIT is not ideal because normal tissues are over-irradiated to ensure that all regions of the tumor are adequately radiated.

Another approach to intensify RIT is to administer additional doses after a response to a single RIT dose. Administration of multiple RIT doses provides better disease control because of the more uniform distribution of the radiation [13] and because it has to be used to titrate the toxicity in each patient [14]. Clinical evidence indicates that a larger total radionuclide dose can be fractionated into different low doses [14] near the non-myeloablative maximum tolerated dose (MTD) [15] or near the myeloablative MTD [16]. DeNardo et al. showed that low-dose fractionated RIT with ^{131}I-Lym-1 (30 or 60 mCi at 2- to 6-week intervals) could induce a response in a patient who had substantial infiltration of the marrow by malignant cells, while still controlling morbidity [14].

On the basis of these observations, the MTD trial of ^{131}I-Lym-1 was designed to determine the amount of ^{131}I-Lym-1 that could be tolerated and to assess the toxicity and efficacy of multiple doses given 4 weeks apart [15]. In the absence of extensive marrow lymphoma or BM reconstitution, the MTD of ^{131}I-Lym-1 was 100 mCi/m^2 (3.7 GBq/m^2) of body surface area (BSA) for each of the first two doses. Two of three patients in the 100 mCi/m^2 cohort tolerated the study maximum of four therapy doses of ^{131}I-Lym-1. Total ^{131}I received by these three patients were 355, 626, and 810 mCi (13.2, 23.2, and 30.0 GBq), which contributed 121, 207, and 275 rad, respectively, to the whole body and 103, 194, and 275 rad, respectively, to the BM [15].

Here, we chose 200 mCi radioiodide as a fixed dose for the first administration of ^{131}I-rituximab in all study patients based on the results of our previous study [4]. The dose of ^{131}I used in the subsequent readministration of ^{131}I-rituximab was modified into one of the following does: 200, 150, or 100 mCi according to the grade of hematological toxicities observed with the previous treatment of ^{131}I-rituximab. A total of 87 therapy doses (median 2; range 1–6) of ^{131}I-rituximab were administered in all 31 patients. The median total dose of ^{131}I administered to each patient over the entire study treatment period was 501 mCi (18.5 GBq; range 198–1,188 mCi [7.3–43.9 GBq]). In other words, the median dose of ^{131}I administered per BSA in each treatment (mCi/m^2) was 115 mCi/m^2 (range 74–149 mCi/m^2). This dose was almost identical to the MTD of 100 mCi/m^2 suggested by DeNardo et al. [15].

A twofold increase in the response rate (68 % from 29 % for a single treatment) and a threefold increase in the median response duration (8.6 months from 2.9 months for the single treatment) were observed in this study. Moreover, the repeated RIT with ^{131}I-rituximab induced a more favorable response and better survival even for patients with an aggressive histology compared to the single RIT with ^{131}I-rituximab.

With respect to toxicities, 72 % of the patients experienced grade 3 or 4 neutropenia and 66 % of the patients experienced grade 3 or 4 thrombocytopenia (Table 3). The incidences of hematological toxicities per patient for the repeated RIT protocol were higher than those for the single treatment with ^{131}I-rituximab, although they were comparable on a per-treatment basis. In addition, the median duration of the grade 3 or 4 toxicities in the repeated RIT protocol was longer than that of the single treatment with ^{131}I-rituximab.

In summary, our data suggest that the efficacy of RIT with ^{131}I-rituximab can increase with repeated administration compared to a single treatment with the same drug in patients who have relapsed or refractory B cell NHL. Repeated RIT with ^{131}I-rituximab induced a more favorable response and better survival for the patients with an aggressive histology compared to a single RIT with ^{131}I-rituximab. The toxicities for repeated RIT were comparable to those for a single ^{131}I-rituximab treatment. Studies on repeated RIT with ^{131}I-rituximab using a higher dose of unlabeled rituximab (250 mg/m^2) are currently underway in order to investigate whether this could enhance the efficacy of the unlabeled cold mAb compared to the dose of cold rituximab (70 mg) used in the present study.

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Conflict of interest None.

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