Radioimmunotherapy with ^{177}Lu-DOTA-Rituximab: Final Results of a Phase I/II Study in 31 Patients with Relapsing Follicular, Mantle Cell, and Other Indolent B-Cell Lymphomas

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The aim of this study was to determine the maximum tolerated dose (MTD) and to explore the clinical response to ^{177}Lu-DOTA-rituximab in the treatment of patients with relapsed follicular, mantle cell, or other indolent lymphomas such as marginal zone lymphoma. **Methods:** To evaluate the MTD, we adjusted the dosage of the radiopharmaceutical according to body surface area (BSA). **Results:** The MTD using ^{177}Lu-DOTA-rituximab was 1,665 MBq/m^2 of BSA. Thrombocytopenia and leukopenia were the dose-limiting toxicities. Significant anemia occurred only at dose level 7 (1,850 MBq/m^2 of BSA). We observed the nadir of platelets after a median of 36 d from treatment and the nadir of granulocytes after a median of 50 d. Median time to recovery to the next lower grade of toxicity was 7 d. Nonhematologic toxicity was negligible. We observed clinical responses at all dose levels and for all lymphoma entities. Some of the responses were durable; the longest follow-up is currently over 8 y. At present, 11 patients are alive and 8 patients are disease-free. **Conclusion:** Our results demonstrate the safety and feasibility of ^{177}Lu-DOTA-rituximab treatment for the lymphoma entities tested in this study.

Key Words: radioimmunotherapy; ^{177}Lu; lymphoma; rituximab

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The chimeric anti-CD20 antibody rituximab is an integral component of treatment for patients with CD20-positive B-cell–derived neoplasms. Rituximab kills lymphoma cells via a mechanism of antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (*1*). Apoptosis may also be triggered independently of antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The addition of this antibody to standard chemotherapy regimens has improved the outcome of many B-cell disease entities and has increased the cure rate, particularly of diffuse large B-cell lymphoma (*2*).

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Radioimmunotherapy combines biologic and radiolytic mechanisms to destroy tumor cells. The crossfire effect of the β-radiation as well as the bystander effect may kill neighboring cells that may not express the target protein or may be poorly vascularized (*3*). Several groups have experimented with radioimmunotherapy in the treatment of malignant lymphoma mainly using ^{131}I or ^{90}Y labeled to various antibodies, some with radiation doses requiring bone marrow support (*4–7*). The 2 most extensively studied radioimmunoconjugates are ^{90}Y-ibritumomab-tiuxetan (Zevalin; Spectrum Pharmaceuticals, Inc.) (*8–11*) and ^{131}I-tositumomab (Bexxar; GlaxoSmithKline) (*12,13*). The ^{90}Y-labeled murine anti-CD20 antibody ibritumomab was the first radiolabeled antibody for cancer treatment approved by the Food and Drug Administration, in 2002 (*14*). In a 2-arm randomized trial, Witzig et al. (*10*) observed a higher response rate in indolent lymphoma after radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan than after rituximab therapy alone. In another phase III study, this compound was found to prolong remission duration after standard chemotherapy in advanced follicular lymphoma (*15*).

^{177}Lu is a low-energy β-emitter (maximum energy, 0.497 MeV) with a relatively short tissue penetration range (maximum, 1.6 mm). Because malignant lymphoma cells often infiltrate normal tissues in a diffuse manner, we decided to use the lower β-energy and shorter tissue penetration of ^{177}Lu as these may result in a more favorable tumor-to-nontumor ratio (*16,17*). In addition, ^{177}Lu emits γ-radiation (113 keV, 7%; 208 keV, 11%) that can be used for scintigraphic imaging, allowing immediate control of distribution and dosimetry in treated patients. The fraction and energy of its γ-emissions are lower than those of ^{131}I (362 keV), whose physical characteristics necessitate a prolonged hospital stay for treated patients in many countries (*18*).

Since therapeutic use of murine antibodies may lead to the development of human antimouse antibodies (*11,19,20*), we decided to use the commercially available chimeric anti-CD20 antibody rituximab. Coupled to ^{131}I, rituximab has been successfully used in the treatment of indolent lymphoma as reported by Leahy et al. (*21,22*). DOTA was used to ensure kinetically stable binding of ^{177}Lu to rituximab as previously described (*23*).

The aim of this study was to determine the maximum tolerated dose (MTD) and to explore clinical response to ^{177}Lu-DOTA-rituximab in the treatment of patients with relapsed follicular, mantle cell, or other indolent lymphomas. There is no consensus on the treatment of such multiply relapsing patients after previous

alkylators, anthracyclins, anti–B-cell antibodies, and antimetabolites. Bendamustin was not available during the study period. Therefore, it was considered to be ethically responsible to offer those patients a phase I trial.

As estimated from preclinical studies, the starting dose was 740 MBq/m^2 of body surface area (BSA). To evaluate the MTD, we adjusted the dose of radiopharmaceutical according to BSA.

MATERIALS AND METHODS

Patient Eligibility

Patients with histologically confirmed relapsed or refractory CD20-positive B-cell lymphoma (follicular lymphoma with or without transformation, mantle and marginal zone lymphoma, or other indolent lymphomas) were included provided they fulfilled the following criteria: age greater than 18 y with a life expectancy of more than 3 mo, not pregnant or lactating, and performance status of 2 or better according to the World Health Organization scale. Within 1 wk of the start of treatment, patients were required to have an absolute neutrophil count above 1.5×10^9/L, a circulating lymphocyte count below 5×10^9/L, a platelet count above 100×10^9/L, a total bilirubin level of no more than 20 μmol/L, an alanine aminotransferase level below 2.5 times normal, and a serum creatinine clearance level above 60 mL/min. A bone marrow biopsy specimen showing less than 25% infiltration by tumor cells was required. Patients who had previously undergone radiation therapy to the pelvis, femora, or lumbar spine or high-dose treatment with stem cell transplantation were excluded.

Any prior treatment had to be completed at least 6 wk before study entry. The study protocol was approved by the local ethics committee. Written informed consent was obtained from all subjects.

Study Design

We conducted a prospective, single-center, open-label phase I/II dose escalation study starting at 740 MBq (20 mCi) of ^{177}Lu-DOTA-rituximab per square meter of BSA. Doses were escalated in the absence of any nonhematologic toxicity of grade 2 or less and if no more than 1 patient showed reversible hematologic grade 4 toxicity. All patients received rituximab, 250 mg/m^2 of BSA, on days 1 and 8. On day 8, the radiopharmaceutical was injected after infusion of the second dose of rituximab. The dose escalation steps were 185 MBq/m^2 of BSA. The MTD was defined as the dose at which at least 1 patient exhibited more than 1 nonhematologic grade 2 toxicity and more than 1 hematologic grade 4 toxicity.

After application of ^{177}Lu-DOTA-rituximab, the patients were hospitalized for 5 d for imaging and, at the highest doses, to fulfill radiation safety requirements. Dosimetry was performed on 20 patients.

Physical examination, performance status, blood chemistry, hematology, and urine analysis were recorded at baseline. Blood tests were performed weekly up to week 10 or until recovery from nadir. Whole-body contrast-enhanced CT and ^{18}F-FDG PET or ^{18}FDG PET/CT was performed at baseline and 8–12 wk after treatment. The International Workshop Criteria and PET-based response criteria were used for response assessment (*24*). Toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 3.0 (*25*).

Radiopharmaceutical

The chimeric anti-CD20 monoclonal antibody rituximab was provided by Roche Pharma (Schweiz) AG. ^{177}Lu was purchased either from I.D.B. Holland BV or from Perkin Elmer. *p*-SCN-benzyl-DOTA was purchased from Macrocyclics, Inc. The compound was prepared as described previously (*23*).

Imaging and Dosimetry

Imaging for analysis of the biodistribution and dosimetry was performed with a dual-head Prism 2000 XP camera (Picker) using parallel-hole, medium-energy, general-purpose collimators. The windows were centered over both ^{177}Lu photon peaks (113 and 208 keV) with a window width of 20%. In all patients, whole-body scans were obtained 1, 2, 4, 24, and 48 h after injection of the radiopharmaceutical, followed by individually planned whole-body scans up to 361 h after injection. Dosimetric calculations were performed on 20 patients. In these patients, blood samples were drawn 5 min and 1, 2, 4, 24, and 48 h after injection and later, individually, up to 361 h after injection. Urine was collected from 3 male patients up to 72 h after injection. Radioactivity in blood and urine was measured with a γ-counter (Cobra II; Canberra Packard). Dosimetry was performed as described previously (*23,26*). The correction factor was taken as 0.35.

Statistical Methods

The duration of neutropenia, thrombocytopenia, or anemia was measured sequentially from baseline to recovery from nadir. Blood counts were measured at least weekly.

Response rates were assessed 10–12 wk after treatment. Patients were then were followed up every 6 mo. Prism 4 (GraphPad Software, Inc.) was used to calculate and generate the Kaplan–Meier plots for overall survival and progression-free survival.

RESULTS

Patient Characteristics

Thirty-one patients were enrolled. Patient baseline characteristics are given in Table 1. Thirteen patients had follicular lymphoma, 1 patient had follicular lymphoma transformed into diffuse large B-cell lymphoma, 14 patients had mantle cell lymphoma, and 2 patients had marginal zone lymphoma. One patient had a history of stage IIA diffuse large B-cell lymphoma treated with CHOP (cyclophosphosphamide, doxorubicin, vincristine, prednisone) and involved-field radiation and had been in a complete remission (CR) for 6 y. This patient had a recurrence with an indolent B-cell lymphoma in the retroperitoneum, not histologically classifiable. The median age was 61 y (range, 36–86 y). The median time from initial diagnosis to radioimmunotherapy was 49 mo (range, 15–190 mo). Patients were extensively pretreated and had received prior chemotherapy with a median of 3 regimens (range, 1–7), and 21 (68%) had received an anthracycline. Ten patients (32%) had received prior external-beam radiation therapy, and 22 (71%) had undergone prior treatment with rituximab. Ten patients (32%) had bulky disease (tumor mass $\geq$ 5 cm in diameter) and 14 (45%) had less than 25% bone marrow infiltration with lymphoma at study entry.

Dose Escalation

Five patients were treated with dose level 1 of ^{177}Lu-DOTA-rituximab (740 MBq/m^2 of BSA). Two patients were treated with dose level 2 (925 MBq/m^2), and 5 patients with dose level 3 (1,110 MBq/m^2). At dose level 4 (1,295 MBq/m^2), 1 patient had rapid disease progression and died after receiving salvage therapy. Therefore, 2 additional patients were included at this dose level. Four patients were treated with dose level 5 (1,480 MBq/m^2), 5 patients with dose level 6 (1,665 MBq/m^2), and 3 patients with dose level 7 (1,850 MBq/m^2).

Dosimetry

Dosimetry calculations from 20 patients resulted in a mean whole-body dose of 8.77 mGy/MBq. The mean absorbed dose to the red marrow was found to be 9.70 mGy/MBq. This indicates that the absorbed dose of radiation for all patients was below 1 Gy to the whole body as well as to the red marrow.

TABLE 1
Demographics and Baseline Characteristics of the 31 Treated Patients

Characteristic	Data*
Age (y)	
Median	61
Range	36–86
Sex	
Male	17 (55)
Female	14 (45)
Performance status (World Health Organization)	
0	16 (52)
1	15 (48)
Ann Arbor stage	
I/II	3 (10)
III/IV	28 (90)
Histology	
Follicular	13 (42)
Follicular, transformed†	1 (3)
Mantle cell lymphoma	14 (45)
Marginal zone lymphoma	2 (7)
Indolent lymphoma, not otherwise specified‡	1 (3)
B symptoms at study entry present	4 (13)
Bone marrow involvement	
None	17 (55)
≤25%	14 (45)
Disease bulk ≥ 5 cm	10 (32)
Previous chemotherapy	
1–3 regimens	18 (58)
≥4 regimens	13 (42)
No prior rituximab treatment	9 (29)
Prior radiation	10 (32)
Response to last treatment before radioimmunotherapy	
Progression	3 (10)
Response (CR, PR, and stable disease)	27 (87)
Not evaluable	1 (3)

*Data are *n* followed by percentage in parentheses, except for age.
†Transformation to diffuse large B-cell lymphoma.
‡Diffuse large B-cell lymphoma treated with curative intent 5 y before diagnosis of indolent lymphoma, not otherwise specified.

Toxicity

Toxicity was mainly hematologic. The hematologic adverse events are summarized in Table 2.

Anemia was minor, with only 1 grade 2 event each at dose levels 4 and 5. Only 1 patient with grade 3 anemia at dose level 7 required erythrocyte transfusions. The nadir was reached at a median of 50 d from baseline (range, 1–78 d). The recovery time to the next lower grade took a median of 7 d (range, 7–56 d).

Grade 3 and 4 neutropenia occurred in 7 patients (23%) starting at dose level 3. One grade 4 event was observed in the last patient entering the study at dose level 7. This patient succumbed to sepsis in neutropenia 2 mo after radioimmunotherapy. Because of his advanced age and comorbidities, the patient received best supportive care without aggressive treatment measures. The median nadir of the neutrophil count was reached after 57 d from baseline (range, 50–78 d). The median time to recovery to the next lower grade was 7 d (range, 7–21 d).

Grade 3 and 4 thrombocytopenia occurred in 7 patients (23%). Grade 3 thrombocytopenia was observed at dose levels 4–6. One brief grade 4 episode occurred in 1 patient at dose level 3, and 1 patient at dose level 7 had a long-lasting grade 4 toxicity without recovery. The nadir was reached after a median of 43 d from baseline (range, 22–57 d). The median time to recovery to the next lower grade was 7 d (range, 7–28 d).

Patients with bone marrow involvement at baseline did not reveal obvious differences in platelet or neutrophil nadirs. After a maximum observation time of 8.5 y, no myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred.

Nonhematologic toxicity was minor, with grade 1 fatigue and nausea on the days after treatment being the most prominent symptoms. No unexpected changes in laboratory values were observed, and no treatment-related organ damage occurred.

Response to Treatment and Clinical Outcome

Tumor response was evaluable in 29 of 31 patients. One patient died before reevaluation. In another patient, ^{18}F-FDG PET/CT scans were not repeated but the patient was evaluable for clinical follow-up. Results are summarized in Table 3.

Surprisingly, responses occurred at all dose levels both in patients with follicular lymphoma and in patients with mantle cell lymphoma. At dose level 1, CR was observed in a patient with follicular lymphoma involving the small intestine and retroperitoneal nodes. After an observation time of 105 mo, this patient has not relapsed. At dose level 2, a durable CR was obtained in a patient with follicular lymphoma with disseminated, partly bulky nodal disease (observation time, 99 mo) (Fig. 1). At dose level 3, CR lasting 7 mo was observed in a patient with mantle cell lymphoma. At dose level 5, CR lasting 25 mo was recorded in a patient with follicular lymphoma. Seven of 8 patients at dose levels 6 and 7 had a response (3 with CR and 4 with partial remission [PR]). In total, responses were observed in 15 of 29 evaluable patients (52%). Six patients (21%) achieved a CR at reassessment, and 9 patients (31%) had PR. The overall response rate was 82% (9/11 patients) in patients with follicular lymphoma and 21% (3/14 patients) in patients with mantle cell lymphoma. One patient with follicular lymphoma achieved a tumor regression of 35%, and 1 patient with mantle cell lymphoma had tumor shrinkage to just below 50%. These reductions in tumor size did not fulfill the criteria for PR according to the International Workshop Criteria and PET-based response assessment (*24*). One patient with mantle cell lymphoma with initial bone marrow involvement had a CR assessed by imaging, but no bone marrow examination was performed after radioimmunotherapy. Therefore, the result was classified as PR.

The response rate for patients without bone marrow involvement at baseline (11/15 patients; 73%) was higher than that for patients with prior bone marrow involvement (4/14 patients; 29%). Patients without prior rituximab treatment had lower response rates (4/9 patients; 44%) than did patients pretreated with rituximab (11/20 patients; 55%). However, 3 patients without prior rituximab treatment showed a response (<30%) not qualifying as PR and 1 patient without further bone marrow examination (described above) achieved a CR as assessed by imaging. Nevertheless, the interpretation of the subgroup analysis should be undertaken with caution.

At the time of this analysis, 11 of 31 patients were still alive. Nineteen deaths were secondary to malignant lymphoma and 1 death was due to radioimmunotherapy-induced neutropenia and sepsis. With a median follow-up of almost 7 y (range, 2 mo–8.5 y), the estimated median time of survival after radioimmunotherapy was 4 y (Fig. 2).

TABLE 2
Hematologic Toxicity Occurring Within Each Dose Group

Grade	Thrombocytes (*n*)	Leukocytes (*n*)	Neutrophils (*n*)
Dose level 1 (740 MBq/m^2): $n = 5$			
1	0	5	1
2	3	0	1
3	0	0	0
4	0	0	0
Dose level 2 (925 MBq/m^2): $n = 2$			
1	0	1	1
2	0	0	0
3	0	0	0
4	0	0	0
Dose level 3 (1,110 MBq/m^2): $n = 5$			
1	0	1	1
2	3	2	1
3	0	1	1
4	1	0	0
Dose level 4 (1,295 MBq/m^2): $n = 7$			
1	1	0	1
2	0	2	2
3	1	2	1
4	0	0	0
Dose level 5 (1,480 MBq/m^2): $n = 4$			
1	0	1	0
2	1	1	1
3	2	2	2
4	0	0	0
Dose level 6 (1,665 MBq/m^2): $n = 5$			
1	1	0	0
2	1	1	1
3	2	3	2
4	0	0	0
Dose level 7 (1,850 MBq/m^2): $n = 3$			
1	1	0	0
2	1	1	1
3	0	0	0
4	1	1	1

The clinical follow-up data were analyzed with a focus on the various lymphoma subtypes treated. Of the patients with follicular lymphoma ($n = 13$), 8 of 13 were alive after a median of 84 mo (range, 32–105 mo) (Fig. 2). Four patients remain in remission without further treatment at over 32, 34, 99, and 105 mo after radioimmunotherapy. Median time to next treatment in the 7 patients requiring therapy was 6 mo (range, 2–44 mo) (Table 4). Five of 13 patients died at a median of 7 mo (range, 2.5–56 mo) after radioimmunotherapy.

All patients with mantle cell lymphoma ($n = 14$) progressed after a median of 6 mo (range, 1–27 mo) and died after a median of 17 mo (range, 13–95 mo) (Fig. 2). Twelve of 14 patients received further treatment after a median of 9 mo (range, 1–26 mo).

Four patients with other histologic lymphoma subtypes entered the study. One patient has been in a CR for over 29 mo, and the other 3 had disease progression on ^{177}Lu-DOTA-rituximab.

DISCUSSION

The main goal of this study was to determine the MTD of ^{177}Lu-DOTA-rituximab used for the treatment of patients with relapsed follicular, mantle cell, or other indolent lymphomas such as marginal zone lymphoma.

The MTD using ^{177}Lu-DOTA-rituximab was 1,665 MBq/m^2 of BSA. Thrombocytopenia and leukopenia were the dose-limiting toxicities. Significant anemia occurred only at dose level 7.

The second aim of our study was to explore the clinical outcome of ^{177}Lu-DOTA-rituximab therapy in patients with pretreated indolent lymphoma. We observed responses at all dose levels and for all lymphoma entities. Some of the responses were durable, the longest follow-up being more than 8 y.

The pattern of hematologic toxicity we observed was similar to that of other radioimmunotherapy compounds used in the treatment of malignant lymphoma, namely ^{90}Y-ibritumomab tiuxetan, ^{131}I-tositumomab, and ^{131}I-rituximab. In a phase II study using the standard dose of ^{90}Y-ibritumomab tiuxetan, Witzig et al. (*27*) observed a nadir for thrombocytes at day 43 and for granulocytes at day 50. Nadirs lasted 14 d for thrombocytes and 10 d for granulocytes.

In a phase II study using 2 cold doses of tositumomab and 1 dose of ^{131}I-tositumomab calculated to a total body dose of 0.75 Gy, Kaminski et al. (*13*) observed that the nadir of platelets occurred a week earlier than that of granulocytes, after 34 and 43 d, respectively. The fact that ^{131}I-tositumomab is administered to a whole-body dose of 0.75 Gy and that we calculated a whole-body absorbed radiation dose of approximately 0.9 Gy at the highest

TABLE 3
Response to Treatment According to Various Patient Subgroups

Characteristic	No. of patients	Overall response rate		CR		Stable disease	Progressive disease
		n	%	*n*	%		
Total number of patients	29*	15	52	6	20	8	6
Age (y)							
≤60	13	7	54	2	15	3	3
>60	16	8	50	4	25	5	3
Histology							
Follicular lymphoma	11	9	82	4	36	1†	1
Mantle cell lymphoma	14	3‡	21	1	7	7§	4
Other lymphomas	4	3	75	1	25	0	1
Bone marrow involvement							
No	15	11	73	5	33	1	3
Yes (<25%)	14	4	28	1	7	7	3
Prior rituximab treatment							
No	9	4	44	3	33	5	0
Yes	20	11	55	3	15	3	6

*Two patients were not evaluable.
†Patient achieved tumor regression of 35%.
‡In 1 patient with initial bone marrow involvement, restaging of bone marrow was not done to confirm CR.
§Two patients achieved tumor regression between 40% and <50%.

injected activity used in our study underlines the comparability of our results with previously published findings.

Our patients were heavily pretreated, having received up to 7 regimens before undergoing radioimmunotherapy. In the phase II study using ^{131}I-tositumomab in nonpretreated patients with follicular lymphoma, hematologic toxicity appeared much lower than in studies with pretreated patients, with only 4 patients experiencing grade IV neutropenia and none with grade IV thrombocytopenia (*28*). Median time to nadir was 29 d for thrombocytes and 47 d for granulocytes. The return to baseline values within 43 and 60 d, respectively, was again shorter in these nonpretreated patients. In a multicenter phase II study using ^{131}I-rituximab, Leahy et al. observed in the first 91 patients that the median time to nadir was 6 wk for platelets and 7 wk for neutrophils (*21*). In the 10-y follow up of 142 patients, platelet nadir was reported to occur somewhat earlier, at 5 wk (*22*).

Although the patient numbers were small and the clinical picture heterogeneous, in our patients bone marrow infiltration did not seem to affect the grade of hematologic toxicity (14/31 patients with involved marrow < 25%). This result is in line with an Australian study of ^{131}I-rituximab in which bone marrow involvement did not appear to affect the incidence of hematologic toxicity (*21*). This result also confirms the observations reported in other dose-finding studies, for example, with ^{90}Y-ibritumomab tiuxetan (*27,29*).

Because of the small number of patients and the relatively short observation period of our study, no definitive conclusions can be drawn concerning the induction of secondary MDS or AML. However, the mean radiation absorbed doses were calculated to be 8.77 mGy/Bq for the whole body and 9.70 mGy/mBq for the red marrow. For an average patient with 1.8 m^2 of BSA, the resulting dose is approximately 0.79 Gy and 0.87 Gy, respectively, at 1,850 MBq of ^{177}Lu-DOTA-rituximab per square meter. Therefore, the possibility of some stem cell damage must be considered. In studies using ^{131}I-tositumomab, the annualized incidence

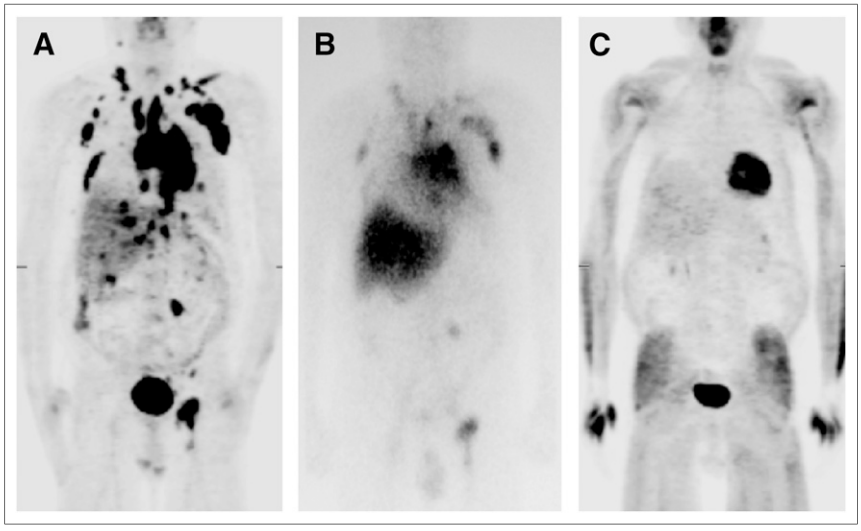

FIGURE 1. Follicular lymphoma in 61-y-old patient with relapsing disease after 4 previous regimens. He was treated with ^{177}Lu-DOTA-rituximab, 740 kBq/m^2, in September 2002. (A) ^{18}FDG PET shows disseminated, partly bulky relapsing disease. (B) ^{177}Lu scintigram 4 d after ^{177}Lu-DOTA-rituximab depicts distribution of ^{177}Lu in tumor masses. (C) Repeated ^{18}FDG PET 2 mo after radioimmunotherapy shows complete remission. Patient has remained in remission since.

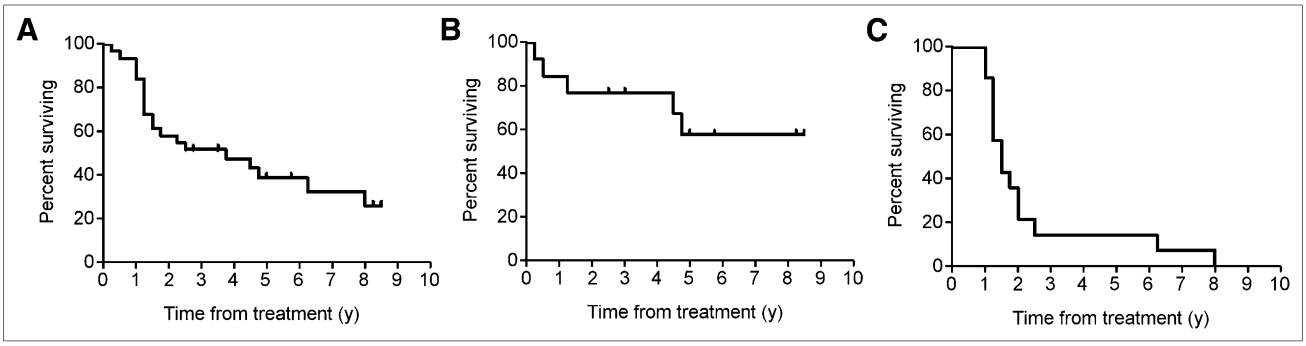

FIGURE 2. Kaplan–Meier survival curves of all patients, patients with follicular lymphoma, and patients with MCL. (A) Overall survival of 31 patients receiving ^{177}Lu-DOTA-rituximab. (B) Overall survival of 13 patients with follicular lymphoma receiving ^{177}Lu-DOTA-rituximab. (C) Overall survival of 14 patients with MCL receiving ^{177}Lu-DOTA-rituximab.

of MDS or AML after a median of 3.2 y was 1.1% per year (*30*). Safety data from patients treated with ^{90}Y-ibritumomab tiuxetan describe 5 cases of MDS in 349 patients (1.4%) and a general risk of 1%–1.5% per year from 2 to at least 9 y after the start of radioimmunotherapy (*11*). Because the incidence of MDS or AML depends on the number and type of previous treatments, it is not surprising that no such cases were reported in 76 patients after ^{131}I-tositumomab was used as initial treatment for follicular lymphoma after a median follow-up of 5.1 y (*28*). Follow-up data after 10 y reported 1 case of MDS about 8 y after treatment (*31*).

Although the initial publication of the FIT study reported just 1 occurrence of AML in the radioimmunotherapy arm, follow-up after a median observation time of 66 mo revealed that MDS or AML occurred in 6 of 207 patients in the ^{90}Y-ibritumomab arm versus 1 of 202 patients in the observation arm (*32*).

Interestingly, clinical responses were observed at all dose levels and in all the lymphoma entities included in this study. We observed CR and PR in mantle cell lymphoma, but these were usually brief. One patient with indolent mantle cell lymphoma responded twice to ^{177}Lu-DOTA-rituximab at dose level 1, but eventually all patients with mantle cell lymphoma relapsed and succumbed to their disease. In a similar manner, nonlabeled rituximab shows some activity in mantle cell lymphoma but the efficacy of this antibody seems to be less pronounced in mantle cell lymphoma than in follicular lymphoma (*33*). The use of radioimmunotherapy in mantle cell lymphoma so far has been disappointing. In a phase II study, 34 patients with relapsed or refractory mantle cell lymphoma were treated with ^{90}Y-ibritumomab tiuxetan and 31% achieved CR or PR. The median event-free survival duration was only 6 mo, and similarly to our findings, all patients relapsed. For those patients achieving a PR or CR, the median event-free survival was 28 mo (*34*). Radioimmunotherapy in mantle cell lymphoma is currently being investigated in the setting of high-dose therapy and stem cell transplantation (i.e., by the University of Nebraska; ClinicalTrials.gov identifier NCT00574509) or as consolidation therapy after induction immunochemotherapy (*35*). Because rituximab was recently shown to prolong remission duration in mantle cell lymphoma (*36*), radioimmunotherapy may also have a place in this clinical setting in the future.

^{177}Lu-DOTA-rituximab appeared to have striking activity in follicular lymphoma, with 9 of 11 heavily pretreated patients responding to radioimmunotherapy. Eight of the 11 patients from our phase I/II study were still alive after a median follow-up of 84 mo. Four of 11 patients are in continuous remission, the longest currently at 105 mo after radioimmunotherapy. Because many studies have emphasized the activity of other radioimmunotherapy compounds in follicular lymphoma (*22,27,28,37,38*), the question of the advantage of ^{177}Lu-DOTA-rituximab versus the other well-known agents will arise. Compared with ^{131}I-rituximab, ^{177}Lu presents less of a radiation hazard to family members and staff. Local radiation safety regulations need to be adapted, since this study is the first in Switzerland using ^{177}Lu bound to an antibody and no specific regulations exist so far. If 1,665 MBq/m^2 of BSA is used in the phase II setting, an overnight stay at the nuclear medicine facility will likely not be necessary or, at most, will be limited to a few days. Thyroid toxicity is not an issue with ^{177}Lu-DOTA-rituximab. Use of the chelator DOTA results in stable binding of

TABLE 4
Time to Next Treatment

Histologic characteristic	No. of patients	Progression/ relapse (*n*)	Next treatment received (*n*)	Time to next treatment (mo)	
				Median	Range
Follicular lymphoma	13	8*	7†	6	2–44.5
Mantle cell lymphoma	14	14	12	9	1–26
Other lymphomas	4	3	3	4	2–17

*One patient was not evaluable.
†One patient had progression without indication for further therapy.

^{177}Lu, so that free (nonlabeled) and potentially toxic radiometal molecules can be excluded (*23*). The use of the chimeric antibody rituximab greatly minimizes the chances of developing human anti-mouse antibodies. Compared with ^{90}Y-ibritumomab tiuxetan, however, cost may be an issue. The total cost of the kit preparation, which can be performed at any nuclear medicine pharmacy, did not exceed $2,000.00. This compound was developed in an academic institution and a patent has not been issued for technical reasons. However, it is obvious that as long as no kit of good manufacturing practice grade is commercially available, the use of the compound will be limited because a certain degree of experience is required to perform a safe treatment in accordance with the local regulations.

If multicenter trials are planned in the future, production of this compound may need to fulfill good manufacturing practice regulations, substantially increasing the cost of individual doses. The same holds true for the kit used in our study.

However, another important advantage of ^{177}Lu-DOTA-rituximab is the kit formulation that was established for this compound. As published previously, the ^{177}Lu-DOTA-rituximab kit can be labeled in a straightforward manner in less than 15 min and with a radiochemical purity of more than 99% (*23*).

During the study period, additional agents such as bendamustine have been investigated for the treatment of indolent lymphomas. Clinicians will now have even more choices to find a sensible treatment sequence for these patients with chronically relapsing disease.

CONCLUSION

This study demonstrated the feasibility of treatment with ^{177}Lu-DOTA-rituximab and that a single course results in a high rate of tumor response in all lymphoma entities and at all dose levels tested. Hematologic toxicity was temporary and manageable, and nonhematologic toxicity was low. Further testing of ^{177}Lu-DOTA-rituximab should therefore focus on indolent B-cell lymphomas, either as a single agent (i.e., for elderly and frail patients) or in combination with immunochemotherapy (i.e., for consolidation). Further dose escalation, despite a probable increase in hematologic toxicity, may be tolerable particularly if this agent is used in the transplant setting for relapsed or high-risk B-cell lymphomas.

DISCLOSURE

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