^{90}Y-Ibritumomab Tiuxetan as Consolidation Therapy After Autologous Stem Cell Transplantation in Aggressive Non-Hodgkin Lymphoma

Roberto Ria[1], Pellegrino Musto[2], Antonia Reale[1], Roberto Guariglia[2], Giuseppe Iodice[1], Franco Dammacco[1], and Angelo Vacca[1]

[1]Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine and Clinical Oncology, University of Bari Medical School, Bari, Italy; and [2]Haematology and Stem Cell Transplantation Unit, Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture, Potenza, Italy

Targeted radioimmunotherapy with ^{90}Y-labeled ibritumomab tiuxetan is a novel therapeutic approach for CD20-positive relapsed or refractory non-Hodgkin lymphoma (NHL). **Methods:** Seven consecutive patients with CD20-positive aggressive NHL who did not fully respond to prior myeloablative chemotherapy were enrolled. A 14.8 MBq (0.4 mCi)/kg dose of ^{90}Y-ibritumomab tiuxetan was administered to all patients, and approximately 100 d afterward ^{18}F-FDG PET/CT was performed to assess response. **Results:** PET/CT showed a complete response in 5 of 7 patients. Of the 2 nonresponsive patients, 1 showed persistent disease and the other progression. Toxicity included thrombocytopenia in all 7 patients and grade IV neutropenic fever in 1 patient. **Conclusion:** Despite the small series studied, we suggest that radioimmunotherapy is safe for consolidation in patients treated with high-dose chemotherapy for aggressive NHL and may provide clinical benefit in extensively pretreated patients.

Key Words: autologous stem cell transplantation; consolidation therapy; non-Hodgkin lymphoma; ^{90}Y-ibritumomab tiuxetan

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Induction therapy aims to produce a maximal response by reducing tumor burden, with the goal of prolonging progression-free survival and overall survival in patients with non-Hodgkin lymphoma (NHL). Residual disease can be eradicated using a myeloablative approach involving high-dose immunochemotherapy with or without radiotherapy, followed by replacement of the patient's stem cells (*1*). Autologous stem cell transplantation (ASCT) plays an established role in patients experiencing a first chemosensitive relapse of aggressive NHL (*2*). However, because disease recurrence is common, additional strategies have been sought to maintain or improve the quality of the initial response.

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For correspondence or reprints contact: Roberto Ria, Department of Internal Medicine and Clinical Oncology, University of Bari Medical School, Policlinico, Piazza Giulio Cesare, 11, I-70124 Bari, Italy.
E-mail: ria@dimo.uniba.it

The introduction of targeted therapeutic approaches, particularly monoclonal antibodies, resulted in considerable success for the treatment of NHL (*3*). Antibodies also represent excellent targeting systems, by the marking of selected cells for interaction with innate immune effector mechanisms or by conjugation with locally delivered moieties of therapeutic value.

^{90}Y-ibritumomab tiuxetan was the first radioimmunotherapy approved for patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL.

Radioimmunotherapy offers several advantages over external-beam irradiation. Normal tissues overlying the tumor mass are not exposed to significant radiation exposure. Because the radioimmunoconjugates are given intravenously, they provide systemic radiation treatment to known or unsuspected tumor cells. Even if radioimmunoconjugates are not truly tumor-specific, growing experience from trials and clinical practice suggests that prolonged normal B-cell depletion is not associated with significant sequelae, so that a narrowly targeted approach is feasible and reasonably safe. Another advantage of radioimmunoconjugates is the relevant bystander effect (*4*).

Radioimmunoconjugates were initially tested as single agents in patients with relapsed indolent and transformed NHL, or at much higher doses with stem cell support, and then in combination with high-dose chemotherapy before ASCT (*5,6*). Radioimmunotherapy consolidation therapy after first-line induction chemotherapy or chemoimmunotherapy in patients with follicular NHL has been evaluated in several trials with good results (*7*).

Here, we describe the effects of radioimmunotherapy as consolidation therapy in a small group of patients with high-risk NHL and residual disease after ASCT.

MATERIALS AND METHODS

Patients

Seven consecutive patients with aggressive NHL who did not fully respond to prior ASCT were included in this controlled, nonrandomized study between November 2005 and September 2008 with the purpose of treating and eradicating any minimal

residual disease. Median age was 47 y, with a range from 36 to 62 y (Table 1). At the time of treatment, bone marrow was lymphoma-free in 5 patients and less than 25% involved in 2 patients. Bone marrow biopsies were performed at the first evaluation after ASCT (100 d after transplantation) and confirmed about 1 mo before radioimmunotherapy. Eastern Cooperative Oncology Group performance status was 0–1 in all patients, and no patient had B symptoms. Lactate dehydrogenase was elevated in 1 patient, and no bulky mass was present. All patients had CD20-positive aggressive NHL: 5 had diffuse large B-cell lymphoma (DLBCL) and 2 had high-risk follicular lymphoma, stage IIIB. All patients received rituximab during their induction treatment, and none showed resistance to immunotherapy. The time from ASCT to treatment with ^{90}Y-ibritumomab tiuxetan ranged from 5 to 10 mo. Standard criteria were required: a baseline platelet count greater than 100,000/mm^3, bone marrow cellularity greater than 15%, and less than 25% lymphomatous involvement of the bone marrow. None of the patients had been given prior total-body irradiation.

The study was approved by the Local Ethical Committee, and all patients gave their informed consent according to the Helsinki Declaration.

Assessment of Minimal Residual Disease

The transplant efficacy was evaluated on day 100 after transplantation by CT and PET/CT, bone marrow biopsy, and clinical and hematologic evaluation. Bone marrow recovery was evaluated by monthly peripheral blood counts. Although patients enrolled in this study had no clinical signs of progressive disease, the persistence of residual disease was established by CT and ^{18}F-FDG PET/CT 100 d after ASCT and was confirmed with a second examination performed after another 2–3 mo.

Treatment Schedule

All patients received radioimmunotherapy 5–10 mo after ASCT. On day 1, patients were given an initial infusion of rituximab, 250 mg/m^2. On day 8, rituximab was once again infused at 250 mg/m^2, followed by 14.8 MBq (0.4 mCi)/kg of ^{90}Y-ibritumomab tiuxetan. Because there is no consensus about the optimal dose of radioactivity to administer to patients after transplantation, we dosed the ^{90}Y-radionuclide on the basis of standard criteria for patients with refractory NHL, in which patients with platelet counts greater than 150,000/mm^3 receive 0.4 mCi/kg and patients with platelets greater than 100,000/mm^3 but no more than 150,000/mm^3 receive 11.1 MBq (0.3 mCi)/kg of ^{90}Y-ibritumomab tiuxetan. All patients were considered to have refractory disease and received 14.8 MBq (0.4 mCi)/kg because of platelet counts greater than 150,000/mm^3, a dose that has been shown to be safe in patients with prior myeloablative chemotherapy (*8*).

Evaluation of Response

Response to ^{90}Y-ibritumomab tiuxetan was assessed by CT and PET/CT. Patients were evaluated 12 wk after treatment. A complete response was defined as elimination of abnormal ^{18}F-FDG PET uptake on CT.

Toxicity

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Pegfilgrastim was administered when the leukocyte count was 2,000/mm^3 or less, and platelet support was initiated when platelets were 20,000/mm^3 or less. In patients developing grade IV neutropenia or thrombocytopenia, the duration of cytopenia was measured from the first day of laboratory evidence of grade IV toxicity until the last day of grade IV toxicity without further support.

RESULTS

Table 2 summarizes the responses and observed toxicities.

Efficacy

Five patients achieved a complete response, as assessed by ^{18}F-FDG PET/CT. A representative patient is shown in Figure 1. All these patients are presently free of disease, with a median duration of response of 4 y (range, 2–5 y), and are on a 6-mo follow-up.

One patient who did not fully respond had a rapid progression of adenopathy 11 mo after ^{90}Y-ibritumomab tiuxetan therapy. This patient was evaluated by CT, which demonstrated new involved lymph nodes in the neck and axilla, also shown by PET/CT. The progression was confirmed by immunohistochemistry of an axillary lymph node. He underwent salvage chemotherapy.

The remaining patient who did not fully respond was given maintenance therapy with rituximab, and a partial response presently persists.

Toxicity

None of the patients experienced dose-limiting toxicity, defined as failure of bone marrow recovery by 12 wk after ^{90}Y-ibritumomab tiuxetan treatment. All patients achieved an absolute neutrophil count of more than 1,000 and a platelet count of more than 25,000 by 12 wk. As a precaution, patients were routinely treated with granulocyte colony-stimulating factor once their total white blood count decreased to 2,000/mm^3 or less (3/7 patients). Nevertheless,

TABLE 1
Patient Characteristics

Patient no.	Age (y)	No. of prior regimens	Time from ASCT to radioimmunotherapy (mo)	Bulky (≥5 cm)	Refractory to rituximab	Bone marrow involvement
1	42	1	6	No	No	No
2	56	1	8	No	No	<25%
3	38	1	5	No	No	No
4	62	2	10	No	No	No
5	41	1	6	No	No	<25%
6	61	2	6	No	No	No
7	36	1	8	No	No	No

TABLE 2
Toxicity and Response

Patient no.	Histology	Toxicity		Blood product support	12th wk		Response
		Absolute neutrophil count < 500/mm^3 (grade IV)	Platelet count < 25,000/mm^3 (grade IV)		WBC count (/mm^3)	Platelet count (/mm^3)	
1	DLBCL	No	No	No	6,300	251,000	CR
2	DLBCL	No	No	No	4,400	78,000	CR
3	Follicular lymphoma	No	Yes	Yes	3,700	243,000	SD
4	DLBCL	No	Yes	Yes	2,100	124,000	CR
5	Follicular lymphoma	No	No	No	7,500	118,000	PD
6	DLBCL	Yes	Yes	Yes	1,900	231,000	CR
7	DLBCL	No	No	No	3,400	86,000	CR

WBC = white blood cell; CR = complete response; SD = stable disease; PD = progressive disease.

1 patient developed grade IV neutropenia. Erythropoietin was administered when the hemoglobin decreased to less than 10 g/dL (2/7 patients), and platelet support was initiated at a level of 20,000/mm^3 or less (3/7 patients). None of the patients received red blood cell transfusions.

Grade IV thrombocytopenia was observed in 2 of 7 patients, grade III in 4, and grade II in 1. No episodes of bleeding were observed. The platelet counts decreased to 20,000/mm^3 or less on days 26, 28, and 32, with recovery to at least 25,000/mm^3 within 4–6 wk. Grade IV neutropenia observed in 1 patient occurred 26 d after ^{90}Y-ibritumomab tiuxetan treatment and lasted 6 wk. No other grade III or IV toxicities were reported.

DISCUSSION

Management of high-risk B-cell NHL has been based largely on the use of chemotherapy and radiotherapy (*1*). In particular, ASCT has an important therapeutic role in patients with aggressive or refractory NHL.

Radioimmunotherapy is also being found to play a prominent role in the treatment of NHL, even if treatment patterns shift from nonspecific cytotoxic agents to targeted cell-specific agents (*9*). Its efficacy has been demonstrated in patients with relapsed or resistant aggressive DLBCL receiving ^{90}Y-ibritumomab tiuxetan treatment, resulting in remarkable response rates and durable responses (*10*). Growing evidence suggests greater benefits from the earlier use of ^{90}Y-ibritumomab tiuxetan, including its administration as first-line therapy or at first relapse (*11*).

Although ^{90}Y-ibritumomab tiuxetan has been evaluated in several patient groups in a variety of settings (*12*), few studies have been published on its use in patients with a history of myeloablative therapy. Jacobs et al. (*8*) suggested that the ^{90}Y-ibritumomab tiuxetan regimen is not more toxic in these patients than in the population with relapsed or refractory NHL without prior myeloablative therapy. In our small group of patients, recovery of neutrophil count to more than 1,000/mm^3 and platelet count to more than 25,000/mm^3 occurred in all by 12 wk after ^{90}Y-ibritumomab tiuxetan treatment. However, in the study of Jacobs et al., only 1 of 7 evaluable patients achieved a complete response lasting 10 mo, indicating that the treatment response was less favorable than reported previously (*13*). In that previous study (*13*), using ^{131}I-tositumomab in patients with previous myeloablative therapy, 7 of 14 patients had an objective response, with 5 patients achieving a complete clinical response. Although these patients were heavily pretreated with chemotherapy

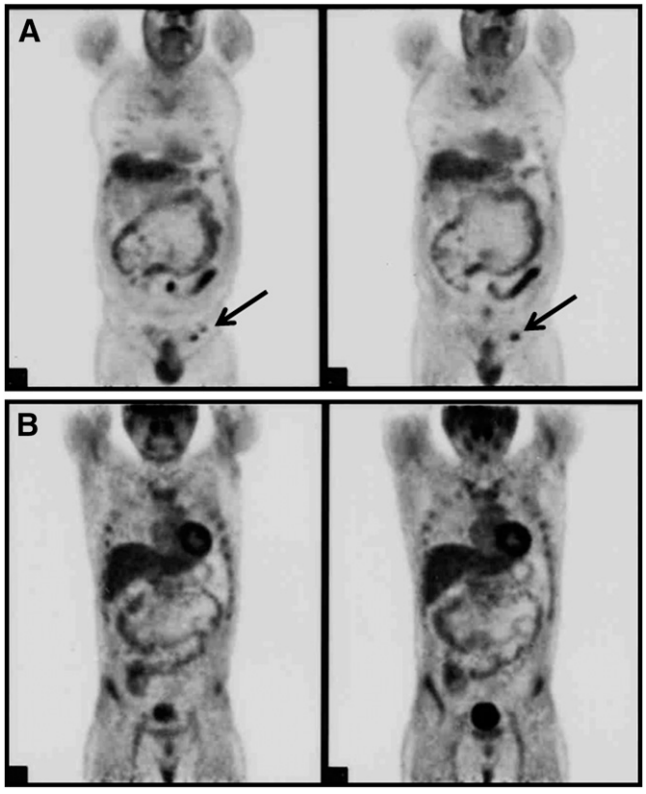

FIGURE 1. Representative PET/CT evaluation showing complete remission of non-Hodgkin lymphoma (arrows) after treatment with ^{90}Y-ibritumomab: pretreatment scan (A) and scan after 12 wk (B).

and had low-grade and intermediate-grade histology, they had not been previously treated with rituximab.

The potential efficacy of radioimmunotherapy in relapsed aggressive lymphoma, its emerging use as consolidation therapy in the first-line treatment of follicular lymphoma, and reports that radioimmunotherapy is more effective when administered earlier in the disease course provide a rationale for the investigation of consolidation radioimmunotherapy after first-line induction therapy in patients with DLBCL (*14*). A phase II trial is currently investigating consolidation treatment with ^{90}Y-ibritumomab tiuxetan after rituximab, cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone (R-CHOP) in elderly patients (≥60 y) with high-risk, untreated DLBCL, because these patients have a high relapse rate and significantly lower progression-free and overall survival rates than younger patients (*15*). Early results have indicated that consolidation radioimmunotherapy has a favorable tolerability profile, with manageable toxicities. In addition, responses improved after consolidation therapy, and overall and progression-free survival rates after a median follow-up of 23 mo were 88% and 80%, respectively. Results are also awaited from 2 ongoing phase II trials investigating ^{90}Y-ibritumomab tiuxetan consolidation therapy in place of external-beam radiation after high-dose CHOP or R-CHOP (ClinicalTrials.gov trial identifier, NCT00070018 and NCT00088881, respectively) (*16*), which, it is hoped, will clarify the extent of the role of ^{90}Y-ibritumomab tiuxetan in DLBCL treatment.

Patients with mantle cell lymphoma have also received benefits from rituximab consolidation therapy after high-dose chemotherapy and ASCT (*17*). Pilot studies with ^{90}Y-ibritumomab tiuxetan in patients with heavily pretreated mantle cell lymphoma have shown promising results, but reports suggest that first-line consolidation radioimmunotherapy after induction chemoimmunotherapy may result in more durable responses (*18*). Similarly, investigators conducting a pilot study of ^{131}I-tositumomab followed by CHOP chemotherapy in 24 patients with mantle cell lymphoma concluded that minimal residual disease was not eradicated by this regimen and proposed the evaluation of consolidation radioimmunotherapy after first-line induction therapy as an alternative (*19*). Subsequently, 2 phase II studies evaluating ^{90}Y-ibritumomab tiuxetan consolidation therapy after R-CHOP or other immunochemotherapy induction regimens have shown a higher extent of response (50% partial to complete response conversion rate), with an associated longer remission duration (*20*). Such emerging results suggest that consolidation radioimmunotherapy is a remarkably effective treatment approach for patients with mantle cell lymphoma.

CONCLUSION

In this pilot study on a small series of patients, we demonstrated that the administration of ^{90}Y-ibritumomab tiuxetan to patients with high-risk NHL with minimal residual disease after ASCT may be an ideal agent for consolidation therapy. Furthermore, the toxicity associated with this approach was minimal. No enrolled patient experienced dose-limiting toxicity after the administration. In addition, overall outcomes were highly encouraging, with a complete response in 5 of 7 patients. Our results suggest that further evaluation to assess the value of ^{90}Y-ibritumomab tiuxetan as consolidation therapy for high-risk NHL, especially in patients who have already received ASCT, is warranted.

DISCLOSURE STATEMENT

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