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

Roberto Ria1, Pellegrino Musto2, Antonia Reale1, Roberto Guariglia2, Giuseppe Iodice1, Franco Dammacco1, and Angelo Vacca1

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

Targeted radioimmunotherapy with 90Y-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 90Y-ibritumomab tiuxetan was administered to all patients, and approximately 100 d afterward 18F-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; 90Y-ibritumomab tiuxetan J Nucl Med 2011; 52:891–895 DOI: 10.2967/jnumed.110.084376

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.

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 radio-
immunotherapy. 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 aggres-
tive 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 90Y-
ibritumomab tiuxetan ranged from 5 to 10 mo. Standard criteria
were required: a baseline platelet count greater than 100,000/ mm3,
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 trans-
plantation 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 18F-FDG PET/CT 100 d
after ASCT and was confirmed with a second examination per-
formed 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/m2. On day 8, rituximab was once again infused at 250 mg/m2,
followed by 14.8 MBq (0.4 mCi)/kg of 90Y-ibritumomab tiuxetan.
Because there is no consensus about the optimal dose of radioactivity
to administer to patients after transplantation, we dosed the 90Y-
radionuclide on the basis of standard criteria for patients with refrac-
tory NHL, in which patients with platelet counts greater than
150,000/mm3 receive 0.4 mCi/kg and patients with platelets greater
than 100,000/mm3 but no more than 150,000/mm3 receive 11.1
MBq (0.3 mCi/kg) of 90Y-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/mm3, a
dose that has been shown to be safe in patients with prior myelo-
ablative chemotherapy (8).

**Evaluation of Response**

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

**Toxicity**

Toxicity was evaluated according to the National Cancer Institute
Common Toxicity Criteria (version 3.0). Pegfilgrastim was admin-
istered when the leukocyte count was 2,000/mm3 or less, and pla-
utelet support was initiated when platelets were 20,000/mm3 or less.
In patients developing grade IV neutropenia or thrombocytopenia,
the duration of cytopenia was measured from the first day of lab-
atory evidence of grade IV toxicity until the last day of grade IV
toxicity without further support.

**RESULTS**

Table 2 summarizes the responses and observed toxic-
ities.

**Efficacy**

Five patients achieved a complete response, as assessed by
18F-FDG PET/CT. A representative patient is shown in Fig-
ure 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 90Y-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 con-
firmed 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
90Y-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 precau-
tion, patients were routinely treated with granulocyte col-
ony-stimulating factor once their total white blood count
decreased to 2,000/mm3 or less (3/7 patients). Nevertheless,
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

<table>
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<th>Patient no.</th>
<th>Histology</th>
<th>Absolute neutrophil count &lt; 500/mm$^3$ (grade IV)</th>
<th>Platelet count &lt; 25,000/mm$^3$ (grade IV)</th>
<th>Blood product support</th>
<th>WBC count (/mm$^3$)</th>
<th>Platelet count (/mm$^3$)</th>
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WBC = white blood cell; CR = complete response; SD = stable disease; PD = progressive disease.

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 90Y-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 90Y-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 90Y-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 90Y-ibritumomab tiuxetan in patients with heavily pretreated mantle cell lymphoma have shown promising results, but reports suggest that first-line consolidation radioimmunotherapy after induction chemoinmunotherapy may result in more durable responses (18). Similarly, investigators conducting a pilot study of 131I-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 90Y-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 90Y-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 90Y-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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