

## Full-Dose <sup>90</sup>Y Ibritumomab Tiuxetan Therapy Is Safe in Patients with Prior Myeloablative Chemotherapy

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**Abstract Purpose:** Targeted radioimmunotherapy with yttrium-90 (<sup>90</sup>Y)–labeled ibritumomab tiuxetan (Zevalin, IDEC–Biogen, San Diego, CA) has shown significant activity in the treatment of relapsed or refractory CD20+ non – Hodgkin’s lymphoma. Eligibility criteria used in phase I trials, and adopted in phase II and III trials, excluded patients with prior myeloablative therapy. We treated eight patients with <sup>90</sup>Y ibritumomab tiuxetan who had prior autologous stem cell transplant, but met all other treatment criteria.

**Experimental Design:** Eight patients with CD20+ non – Hodgkin’s lymphoma had extensive prior therapy including myeloablative chemotherapy but did not receive total body irradiation. Each had bone marrow cellularity of >15%, platelet count of >100,000/mm<sup>3</sup>, and one had documented lymphomatous bone marrow involvement of <25%. The standard course of 0.3 to 0.4 mCi/kg of <sup>90</sup>Y ibritumomab tiuxetan was administered to patients at full dose. 18-Flouro-deoxyglucose positron emission tomography/computed tomography scans were done at pretreatment and ~12 weeks after treatment to assess patient response. Maximum toxicities were monitored and classified according to the Common Terminology Criteria for Adverse Events (ver. 3.0).

**Results:** Toxicities observed included grade 4 thrombocytopenia in three of eight evaluable patients and grade 4 neutropenia in one of eight evaluable patients. One patient had a neutropenic fever; all patients were off blood product support 12 weeks post-zevalin. Complete response by 18-flouro-deoxyglucose positron emission tomography/computed tomography imaging occurred in one of seven evaluable patients and one patient treated as consolidation had no evidence of disease.

**Conclusion:** Our experience suggests that <sup>90</sup>Y ibritumomab tiuxetan treatment is safe for use in patients with prior myeloablative therapy when the general inclusion criteria are fulfilled. In this small series, the response rates, however, are limited. Nevertheless, <sup>90</sup>Y ibritumomab tiuxetan treatment may provide clinical benefit in carefully selected extensively pretreated patients.

Yttrium-90 ibritumomab tiuxetan was approved by the Food and Drug Administration on February 12, 2002, and was the first radioimmunotherapy approved for use in the U.S. (1). It was indicated for patients with relapsed or refractory low-grade, follicular, or transformed B cell non–Hodgkin’s lymphoma. Witzig et al. have extensively evaluated the safety of this therapy in a multicenter review of 349 patients (2). The primary associated toxicities were acute and reversible cytopenias. In the trials leading to Food and Drug Administration approval of <sup>90</sup>Y ibritumomab tiuxetan, participation was restricted to patients with “adequate” bone marrow reserves, defined as >15% cellularity,

<25% lymphomatous involvement in the bone marrow, and no history of myeloablative therapy.

The result of such limitations has been a relative contraindication of the drug for patients who, although possessing all other qualifying criteria, have previously failed high-dose chemotherapy followed by an autologous stem cell transplant (HDC-ASCT). As far as we have been able to determine from the literature, no study has evaluated the results of treating post-HDC-ASCT patients with <sup>90</sup>Y ibritumomab tiuxetan. Given the late position of HDC-ASCT in the typical treatment arm of a low-grade lymphoma patient, these patients have few options for further treatment. A novel therapy such as radioimmunotherapy with a unique mechanism of action might offer significant palliation to this group of heavily pretreated patients.

In previous reports, post-HDC-ASCT patients have been observed to respond to immunotherapy. McLaughlin et al. (3) treated 23 patients with low-grade follicular lymphoma who had relapsed after high-dose chemotherapy with ASCT with rituximab and reported an overall response rate of 78%. In another study, Kaminski et al. treated patients with low-grade and transformed B cell lymphoma who had prior ASCT with

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$^{131}\text{I}$ -tositumomab (Bexxar, Corixa Corp, South San Francisco, CA and GlaxoSmithKline, Philadelphia, PA; refs. 4, 5). He observed moderate, reversible myelosuppression and noted that supportive intervention was seldom required, even in post-ASCT patients, although in this latter group, the maximum dose of  $^{131}\text{I}$ -tositumomab was only 60% of the standard dose. Seven of 14 patients responded, with 5 patients achieving a complete response. As a result, we hypothesized that given the similarities in toxicity between the  $^{131}\text{I}$ -tositumomab and  $^{90}\text{Y}$  ibritumomab tiuxetan treatments, we should be able to safely treat post-HDC-ASCT patients with  $^{90}\text{Y}$  ibritumomab tiuxetan.

## Materials and Methods

**Patients.** Eight patients were identified for this study between April 2002 and May 2004. Eligibility criteria included a diagnosis of relapsed or refractory CD20+ non-Hodgkin's lymphoma, and at least three prior regimens of treatment, in seven of the eight patients, the most recent regimen was HDC-ASCT. Time from HDC-ASCT to treatment with  $^{90}\text{Y}$  ibritumomab ranged from 4 to 62 months. With the exception of the lack of prior myeloablative chemotherapy, all other standard criteria for  $^{90}\text{Y}$  ibritumomab were required, including baseline platelet count of  $>100,000/\text{mm}^3$ , bone marrow cellularity  $>15\%$ , and lymphomatous involvement in the bone marrow of  $<25\%$ . Patients who had prior total body irradiation were excluded. All patients gave written informed consent at the time of study entry.

The patient characteristics are shown in Table 1. The median age was 52 years with a range from 36 to 75. The number of prior radiation or chemotherapy regimens ranged from three to seven, with a median of four. Seven of the eight patients had lymphoma-free bone marrow at the time of treatment, and the remaining patient had lymphomatous involvement in the bone marrow of  $<25\%$ . All patients were refractory to rituximab. Eastern Cooperative Oncology Group performance status was  $<2$  in all patients and five patients had B symptoms. Lactate dehydrogenase was elevated in three of seven patients and at least one bulky mass of  $>5$  cm was present in six of eight patients.

Toxicity was evaluated using the National Cancer Institute's Common Toxicity Criteria (version 3.0). In this group of patients, pegfilgastim was initiated at a leukocyte count of  $2,000/\text{mm}^3$  and platelet support was initiated once the platelet count decreased to  $20,000/\text{mm}^3$ . In patients developing grade 4 neutropenia or thrombocytopenia, the duration was measured from the first day of laboratory evidence of grade 4 toxicity until the last value of grade 4 toxicity without further support.

**$^{90}\text{Y}$  Ibritumomab tiuxetan therapy.** Patients identified for this study were administered the standard regimen of  $^{90}\text{Y}$  ibritumomab tiuxetan. On day 1, patients were given an initial infusion of  $250 \text{ mg}/\text{m}^2$  of rituximab followed within 4 hours by an imaging dose of 5 mCi ( $170\text{-}200/\text{mbg}$ )  $^{111}\text{In}$ -labeled ibritumomab tiuxetan. Patients were then evaluated after 24 and 48 (72) hours by whole-body gamma camera imaging to ensure acceptable biodistribution. The therapeutic regimen was given on day 8. Rituximab was once again infused at  $250 \text{ mg}/\text{m}^2$  and followed by 0.3 to 0.4 mCi/kg of  $^{90}\text{Y}$  ibritumomab tiuxetan. Dosing of the  $^{90}\text{Y}$  radionuclide was based on standard criteria, patients with platelet counts of  $>150,000/\text{mm}^3$  received a dose at 0.4 mCi/kg, and patients with platelets  $<150,000/\text{mm}^3$  but  $>100,000/\text{mm}^3$  received a dose of 0.3 mCi/kg. The only exception to this protocol was in the case of the first patient treated, who despite adequate platelet count, was administered 0.3 mCi/kg  $^{90}\text{Y}$  as a precaution. In no case was a total dose of  $>32$  mCi  $^{90}\text{Y}$  administered.

**18-Flouro-deoxyglucose positron emission tomography/computed tomography imaging.** Response to the ibritumomab tiuxetan regimen was evaluated by use of homologous scans by computed tomography (CT) and 18-flouro-deoxyglucose positron emission tomography (PET). Patients were scanned at baseline and again at 12 weeks posttreatment. A partial response was defined as shrinkage of the lymphomatous area by at least 50% over the 12-week period, and a complete response was defined as elimination of abnormal 18-flouro-deoxyglucose-PET uptake and associated structures on CT. As previously published, a complete response by such analysis is predictive of a favorable clinical course (6–8).

## Results

Table 2 summarizes the responses and observed toxicities in this patient population. Of the eight patients identified for this study, three had a diagnosis of follicular lymphoma, four had a diagnosis of transformed/diffuse large B cell lymphoma, and one had a diagnosis of mantle cell lymphoma. All patients were evaluable for toxicity, but only one was non-evaluable for response.

In the nonevaluable case, the patient recurred following HDC-ASCT with large malignant pleural effusion. The patient had a thoracentesis and was treated with a fludarabine-based regimen with clearing of the effusion. Because of the aggressive course of the patient's disease, as evidenced by the short duration of response to HDC-ASCT, he was immediately treated with  $^{90}\text{Y}$  ibritumomab tiuxetan as consolidation rather than waiting for relapse. Because of the absence of evaluable disease at the time of  $^{90}\text{Y}$  treatment, he was included in the study to assess toxicity only.

**Table 1.** Patient characteristics

Patient	Age	Prior regimens	HDC* to radioimmunotherapy (mo)	Bulk (5 cm)	Rituximab (refractory)	Lactate dehydrogenase	Bone marrow involved
1	75	4	62	yes	yes	Hi	no
2	52	5	18	yes	yes	N/A	no
3	47	4	16	no	yes	NL	no
4	46	4	22	no	yes	NL	no
5	70	7	26	yes	yes	Hi	yes
6	70	3	4	yes	yes	NL	no
7	36	4	13	yes	yes	Hi	no
8	71	4	23	yes	yes	NL	yes

\*High-dose chemotherapy with autologous stem cell transplant.

**Table 2.** Summary of toxicity and response

Patient	Histology	Toxicity		Blood product support	12 Weeks		Response
		Absolute neutrophil count (grade 4)	Platelets (grade 4)		WBC	Platelets	
1	DLBC	no	no	no	6.3	346	PD
2	DLBC	no	no	no	4.4	62	PD
3	FL	no	yes	yes	3.7	137	CR
4	FL	no	yes	yes	2.1	42	NED (15+ mo)
5	FL	no	no	no	7.5	88	MR
6	DLBC	yes	yes	yes	1.9	34*	PD
7	DLBC	no	no	no	3.4	169	PD
8	MCL	no	no	no	3.2	45	PD

NOTE: DLBC, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; PD, progressive disease; CR, complete response; MR, mixed response; NED, no evidence of disease. Absolute neutrophil count (grade 4),  $<500/\text{mm}^3$ ; platelets (grade 4),  $<25,000/\text{mm}^3$ .

\*Started palliative radiation therapy at week 9.

**Toxicity.** None of the eight patients treated experienced a dose-limiting toxicity defined as failure of bone marrow recovery by 12 weeks post-zevalin (see Table 2). However, two patients were hospitalized. One patient with extensive mediastinal disease and rapid progression developed a pericardial effusion which required drainage. A second patient was hospitalized with neutropenic fever and a bowel obstruction from disease progression. This patient began palliative radiation to a large abdominal mass 9 weeks after  $^{90}\text{Y}$  ibritumomab tiuxetan. No episodes of bleeding were observed, and all patients, even those requiring transfusions, recovered to an absolute neutrophil count of  $>1,000$  and platelet count of  $>25,000$  by 12 weeks; however, full recovery to pretreatment blood counts was not possible to assess as nonresponding patients received additional treatments. As a precaution, patients were routinely treated with pegfilgastim once their total white blood count decreased to  $2,000/\text{mm}^3$  (four of eight patients). Despite this, one patient developed grade 4 neutropenia. Erythropoietin was administered to patients when the hemoglobin decreased to  $<10$  g/dL (three of eight patients) and platelet support was initiated at a count of  $20,000/\text{mm}^3$  (three of eight patients). One patient received RBC transfusions.

Grade 4 thrombocytopenia was observed in three of eight study patients. The platelet counts decreased to  $20,000/\text{mm}^3$  or below on days 28, 29, and 35 with recovery to a platelet count  $>25,000/\text{mm}^3$  without support within 4 to 7 weeks. Grade 4 neutropenia was observed in this study in one of eight of the evaluable patients. This occurred 22 days after  $^{90}\text{Y}$  ibritumomab tiuxetan and lasted for 7 weeks. No other grade 3 or 4 toxicities were reported.

**Efficacy.** Seven patients with evaluable disease entered this study. One patient achieved a complete response assessed by 18-flouro-deoxyglucose-PET/CT imaging. The response lasted for 10 months before regrowth of disease. Before and after treatment 18-flouro-deoxyglucose-PET/CT scans are shown in Fig. 1. One patient had an early mixed response with adenopathy in the neck and mediastinum regressing, whereas bulky intraabdominal disease remained unchanged. By 12 weeks post-zevalin, the disease began to progress. The patient with nonevaluable disease who was treated as consolidation had no evidence of disease 15+ months post-zevalin. All three of

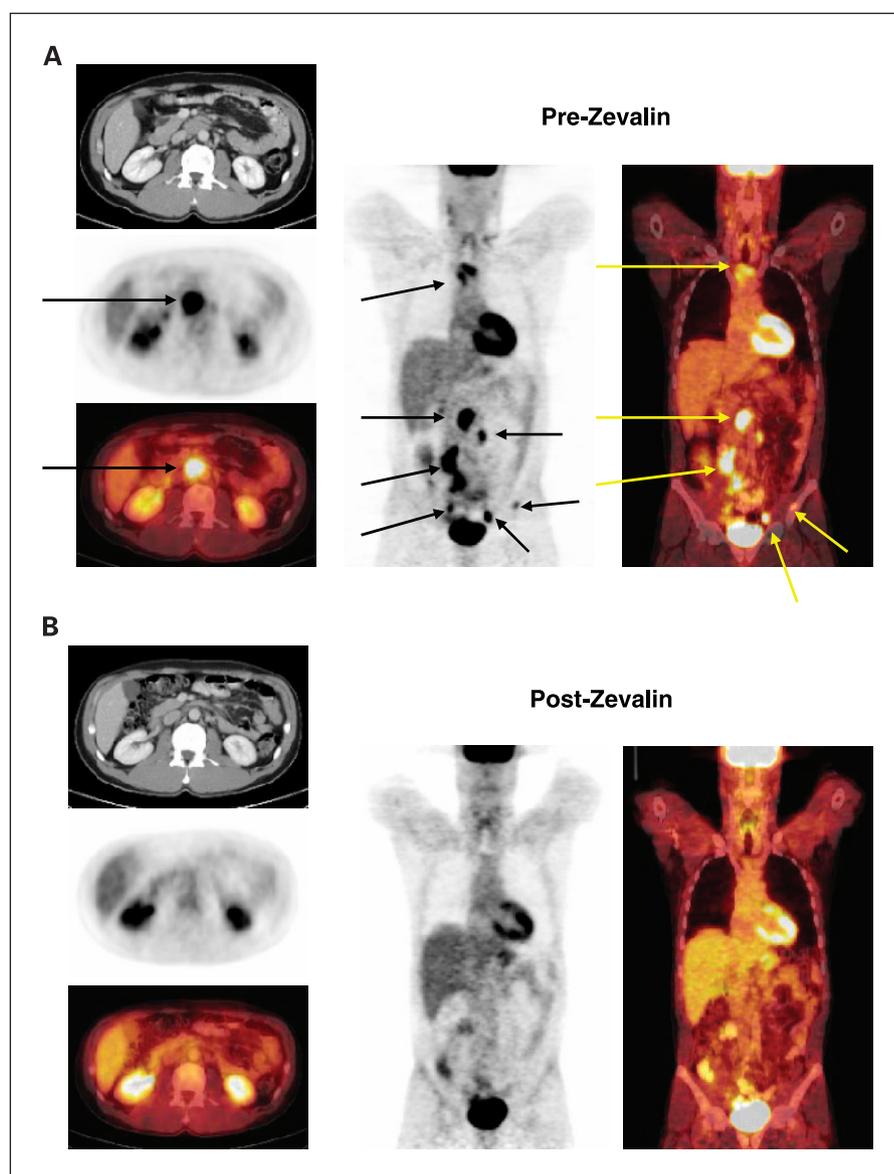
these patients had follicular histology. The patients with transformed/diffuse large B cell lymphoma ( $n = 4$ ) and mantle cell lymphoma ( $n = 1$ ), all had rapid progression.

## Discussion

Although  $^{90}\text{Y}$  ibritumomab tiuxetan has been evaluated in several patient groups in a variety of settings, no available studies exist on its use in patients with a history of myeloablative therapy. Our data suggest that the  $^{90}\text{Y}$  ibritumomab tiuxetan regimen is no more toxic in this group of patients than it is in the relapsed or refractory non-Hodgkin's lymphoma population without prior myeloablative therapy. In the study by Witzig et al. (2), 63% of their patients ( $n = 349$ ) experienced grade 3 or 4 thrombocytopenia, and 59.6% had grade 3 or 4 neutropenia. Furthermore, 10% of patients had a neutrophil count of  $<1,000/\text{mm}^3$  and 11% of patients had a platelet count of  $<50,000/\text{mm}^3$  12 weeks after  $^{90}\text{Y}$  ibritumomab. Failure to achieve hematologic recovery to these levels occurred in patients who either received subsequent therapy or died. In our study, three of eight patients had grade 4 thrombocytopenia and only one patient had a grade 4 neutropenia. In our small group of patients, recovery of neutrophil count to  $>1,000/\text{mm}^3$  and a platelet count of  $>25,000/\text{mm}^3$  occurred in all patients by 12 weeks post- $^{90}\text{Y}$  ibritumomab. The treatment response in this patient group seems to be less favorable compared with the previous report in the literature. One out of seven evaluable patients achieved a complete response lasting for 10 months.

It is of interest that in the study from Kaminski et al. (4) using  $^{131}\text{I}$ -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 and had low-grade and intermediate grade histology, they were not previously treated with rituximab. A number of studies with radioimmunotherapy suggest that the amount of prior therapy, does affect the overall response rate and duration of response. In another study of 76 patients with low-grade, follicular, or transformed B cell lymphoma without prior chemotherapy or immunotherapy, Kaminski et al. reported complete and overall response rates of 75% and 95%, respectively, with a median

**Fig. 1.** *A*, pretreatment PET/CTscan. *B*, 12-week PET/CTscan showing a complete remission following  $^{90}\text{Y}$  ibritumomab. The response was evaluated by use of a hybrid PETand CTscanner. The patient was scanned at baseline and again at 12 weeks posttreatment. After fasting for at least 4 hours, the patient received 12 to 15 mCi F-18 fluorodeoxyglucose i.v. and was scanned after an uptake period of ~ 60 minutes. A diagnostic CTscan with oral and i.v. contrast was acquired, followed by a three-dimensional PETemission scan. PET/CT imaging was obtained from the base of the skull to the groin. The CT and PETscans were visually analyzed for anatomic and metabolic abnormalities on a PET/CT image fusion workstation.



progression-free survival of 6.1 years (9). Witzig et al. (10), using  $^{90}\text{Y}$  ibritumomab in 73 patients with prior chemotherapy, but naïve to immunotherapy, achieved complete and overall response rates of 30% and 86%, respectively. The median duration of response was 14.2 months. In another study by Witzig et al. (11), again using  $^{90}\text{Y}$  ibritumomab but in patients with prior chemotherapy and rituximab, he reported complete and overall response rates of 14% and 70%, respectively. The median duration of response was only 6.4 months.

Although the number of patients available to us for participation in this study was small, our results merit wider

consideration of  $^{90}\text{Y}$  ibritumomab tiuxetan or other radioimmunotherapies as a therapeutic option in selected patients with prior myeloablative therapy. Although several recent studies (12–14) suggest that there is a very high complete response rate when radioimmunotherapy is used sequentially with chemotherapy in previously untreated patients, there is a large group of patients with previously treated non-Hodgkin's lymphoma who are being considered for radioimmunotherapy. In this group of patients with prior therapy, it will be important to find agents that might potentially improve the efficacy of radioimmunotherapy without adding to the hematologic toxicity.

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